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1. Stephens, V. C., *et al.:* J. Am. Pharm. A. (Scient. Ed.), *48*:620, 1959.
2. Salitsky, S., *et al.:* Antibiotics Annual, p. 893, 1959-1960.
3. Reichelderfer, T. E., *et al.:* Antibiotics Annual, p. 899, 1959-1960.
4. Kuder, H. V.: Clin. Pharmacol. & Therap., in press.

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Information for AUTHORS

The Editors of POSTGRADUATE MEDICINE will be pleased to consider original papers in the fields of general medicine, as well as all the specialties, so presented as to be of value and interest to practicing physicians.

Papers should be typewritten, double spaced, and the original, not a carbon copy, should be submitted. Tissue weight paper should not be used. It is suggested that manuscripts comprise a maximum of approximately 3000 words. Authors' full names, academic or professional titles, and complete addresses should be given.

Bibliographies should be kept to a minimum and typed on separate sheets. References should include the author's full name, complete title of article, abbreviated name of journal, volume number, first page and year. References to books, monographs and pamphlets should include the author, title, name and city of the publisher, year of publication, edition and page number of the reference. References should be numbered consecutively throughout the paper and listed in order by number from the text.

POSTGRADUATE MEDICINE stresses the use of appropriate illustrative material suitable for good reproduction. All costs for black and white reproduction are routinely assumed by The Journal. Illustrations should be identified by number and author's name and the top indicated. They must be accompanied by legends numbered to correspond and the position in the text indicated.

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All correspondence pertaining to editorial matters should be addressed to the Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

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Orinase (grams/day)

6/12/57	2.0
8/7/57	1.0
10/2/57	1.0
11/29/57	1.0
1/17/58	3.0
2/14/58	3.0
3/28/58	2.0
5/5/58	1.5

Actual doses used to maintain optimum control in patient J.S., male, age 54[1]

For those diabetics who won't stick to their diets, add appetite-suppressing ***Didrex***† *(benzphetamine, 50 mg. per tablet).*

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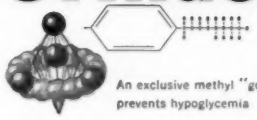

An exclusive methyl "governor" prevents hypoglycemia

Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• CHRONIC DIARRHEA

Q. A 62 year old woman has had diarrhea alternating with constipation for 10 years. Although the condition had been controlled quite well medically, three months ago she began having very loose stools. At present she has four to five stools of brownish liquid a day. In the past, she had been told that she had a "nervous" colon.

The physical examination yielded normal findings. Laboratory data were as follows: hematocrit 45 per cent, hemoglobin 16 gm., white blood cell count 5600, segmented cells 56, band cells 2. lymphocytes 34, monocytes 2, eosinophils 2, and sedimentation rate 10 mm. per hour. Results of the Wassermann test and urinalysis were negative.

Roentgenographic examination of the gallbladder and the upper part of the gastrointestinal tract and administration of a barium enema revealed no pathologic condition. The proctoscopic examination also gave normal findings, and there was no evidence of spasm or lesions of the rectosigmoid. However, a heavy infestation of *Endamoeba coli* was present in specimens of stool.

I am not convinced that this patient's problem is completely functional, and I wonder if infection with *E. coli* could be causing the trouble. Although *E. coli* is considered a nonpathogenic species, I believe there have been cases in which the diarrhea has stopped following eradication of this parasite. If this is true, what therapeutic regimen should be followed?

M.D.—Wisconsin

A. The only pathogenic ameba is *E. histolytica.* When only a nonpathogenic ameba, such as *E. coli,* is found in a patient whose intestinal symptoms are promptly controlled by true antiamebic treatment, it may be assumed that *E. histolytica* was present but was not identified.

There is no objection to and only minimal risk in giving a trial course of carbarsone in a dosage of 0.25 gm. three times a day for five days. This treatment should be stopped for seven days and then repeated.

• SALMONELLA CARRIERS

Q. What is the best method of treating persons who are carriers of *Salmonella typhosa* and of other types of *Salmonella* organisms?

M.D.—Mexico

A. The management of carriers of *Salmonella* organisms, including those harboring *S. typhosa,* is not universally successful. Methods of management can be either medical or surgical. Chloramphenicol is probably the best agent to use in attempting to rid a carrier of *S. typhosa.* If the carrier state consists of a purely enteric residence of other *Salmonella* organisms, oral administration of neomycin and polymyxin may be helpful; when there is evidence of a systemic nidus of the organisms, treatment with tetracycline and streptomycin is preferable.

If the presence of a nidus in an organ is substantiated and if it persists despite medical therapy, surgical treatment may be considered. Cholecystectomy has effected the disappearance of *Salmonella* organisms in some carriers. Systemic nidi of the pathogens also have been located in other organs such as the spleen and the kidneys.

It should be remembered that an appreciable number of carriers, particularly of the so-called convalescent type, ultimately cease to excrete the pathogens even in the absence of therapy. Conversely, some persons continue to be carriers despite all attempts at therapy.

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relieves not only the cough . . . but clears the entire breathing apparatus all-day or all-night with a single oral dose*

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indications:

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DURABOND,® the only long-acting principle proven by radioactive tracer studies in human blood levels. (Bogner, R. L., and Moses, C.: Evaluation of a Sustained Release Principle in Human Subjects Utilizing Radioactive Technique, to be published, 1960.)

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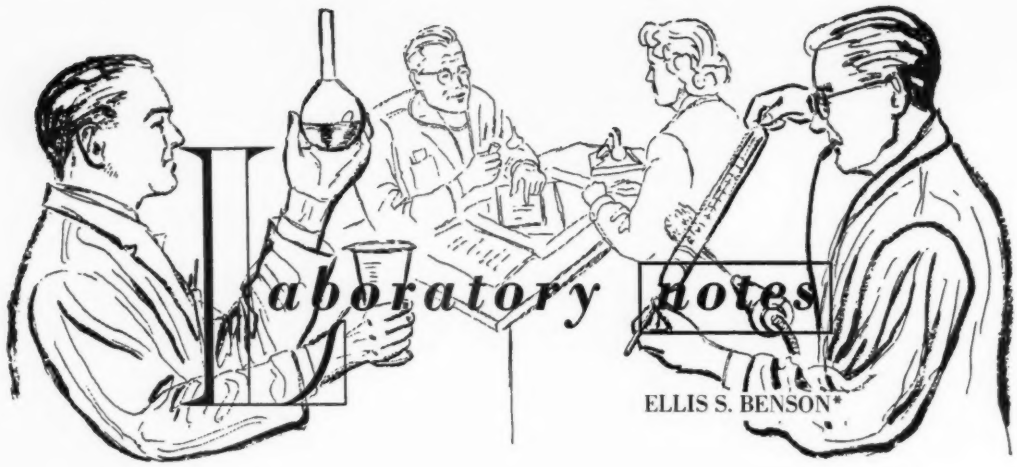

ELLIS S. BENSON*

"The Importance of Cytology to the Practicing Physician"

RECENTLY, a brochure, "The Importance of Cytology to the Practicing Physician," has been prepared under the auspices of the College of American Pathologists and made available to physicians.

In order to illustrate the importance of the subject of this brochure, I have obtained permission to quote its introductory paragraphs:

"At present, cervical cancer is the second most common cause of death from cancer among women. Theoretically, cancer of the uterine cervix is almost 100 per cent curable but, actually, only 40 per cent of patients are being cured. As every physician knows, cure of the patient with cervical cancer can be achieved only if the disease is diagnosed in an early stage. Fortunately, diagnostic techniques in cytology afford a method of diagnosis of early cancer. By means of cytology, an early lesion may be detected long before the disease has caused any signs or symptoms.

"The usefulness of cytology in the diagnosis of cervical cancer has been well established. For example, a recent study in Memphis, Tennessee, covering the findings in 108,000 women who were examined, disclosed 393 intraepithelial carcinomas, of which 353, or 90 per cent, had not been suspected, and 373 invasive carcinomas, of which 112, or 30 per cent, were unsuspected. From the results of this and other studies, it seems obvious that cytologic tests should be made available to more patients.

"Inasmuch as the evaluation of exfoliated cells is a highly specialized diagnostic service, periodic examination (case-finding) of the entire population is an enormous undertaking. There are, however, enough pathologists qualified in cytology in this country to make this useful adjunct to diagnosis available to every physician.

"In addition to its effectiveness, two other aspects of the cytologic method make it extremely helpful to the physician. First, it is a simple office procedure and, second, it is inexpensive for the patient in terms of periodic health examination.

"Cytologic evaluation is somewhat more complex, but is extremely useful in the diagnosis of neoplasms of the lung and stomach. The effectiveness of the method for the detection of cancer in other sites is more equivocal. In any case, cytologic techniques afford a means for the diagnosis of cancer sufficiently

(Continued on page A-26)

*Director of Hospital Laboratories and Associate Professor of Clinical Laboratory Medicine and of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

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as proof accumulates

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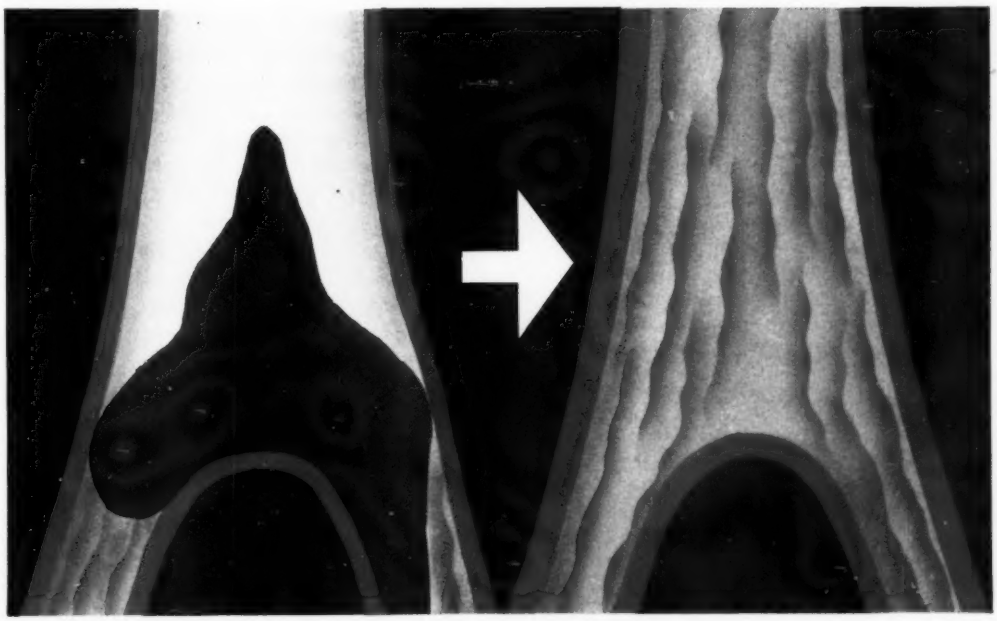

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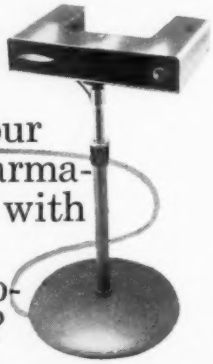

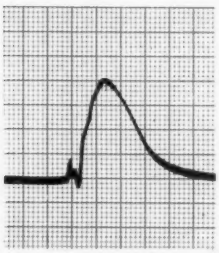

Illustrated (left) is a typical record of a hypothyroid patient — the tracing was taken with a Burdick EK-III Electrocardiograph although any standard ECG may be used. The entire procedure—positioning the patient, connecting the Photomotograph to the ECG, tapping the Achilles tendon, checking the results — takes only a few minutes.

To measure and interpret the tracing is a quick, simple procedure. The technic is quickly mastered, and the results are reliable.

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early to increase significantly the probability of cure."

In following paragraphs, methods of collecting material are cited, including vaginal and cervical aspirations and cervical scraping. Instructions for preparing and fixing cell films of this type of material are given. Instructions are detailed for collecting and handling bronchial material, including sputum, and fluids from the pericardiac, pleural and peritoneal cavities, joint spaces, nipples and stomach.

The application of these methods is briefly discussed, and comments are made concerning the interpretation of results. A number of clear and helpful illustrations are included.

Clearly, cytologic methods of screening are established tools of great value in the detection of both early and incipient cancer. This brochure summarizes for the physician how he can best avail himself of these tools in the conduct of his practice. The brochure was prepared with the assistance of the Field Investigations and Demonstrations Branch of the National Cancer Institute, and is said to be based on the opinions and the combined experience in exfoliative cytology of leaders in research and education in this country.

Finally, an individual rather than a mass, impersonal approach to the subject is stressed:

"The best interests of the patient are served when the practicing physician who obtains the cellular material has close liaison with the pathologist who interprets the slide. False negative and false positive readings can best be detected as a result of close cooperation between the clinical physician and the pathologist who interprets the slides. The objective of adequate screening and cytologic reading cannot be accomplished by application of mail-order methods in large cytologic centers. The cellular material always represents an individual patient, and the problems of diagnosis and therapy must be applied to the patient on an individual basis. In all instances, close liaison between the pathologist and the physician can lead to an equitable solution of the individual problems."

Copies of this important brochure may be obtained by writing to the College of American Pathologists, Prudential Plaza, Chicago.

What's happening in Medicine ?

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

SUBTOTAL GASTRECTOMY FOR ULCER

American College of Gastroenterology:

• A review of 300 subtotal gastrectomies for duodenal ulcer showed that results were good in 34.3 per cent, fair in 44.3 per cent, and poor in 21.4 per cent. Only 50.3 per cent of the patients returned to their original work; 33.7 per cent took lighter jobs, and the remainder did not return to work in post-operative periods ranging from 1 to 11 years. From these results, the procedure can be considered unsatisfactory.—Dr. Rowland Ricketts, Merchantville, N. J.

ALLERGIC CAUSE IN CHEST DISEASE

Kentucky State Medical Association:

• In obscure cases of pneumonitis in which no generalized systemic disease is found, the possibility of an allergic cause should be kept in mind. Even in well-recognized cases of emphysema, chronic bronchitis, and cardiac disease accompanied by pulmonary failure an underlying allergic cause occasionally is encountered. Extrinsic asthma can be detected by intracutaneous skin tests in at least 95 per cent of cases.—Dr. Armand E. Cohen, University of Louisville School of Medicine, Louisville.

NEUROLOGIC FUNCTIONING IN CARDIACS

Symposium, Galesburg (Illinois) State Research Hospital:

• Neurologic, psychiatric and extensive psychologic examinations were performed before and after cardiac surgery in 75 patients. Follow-up studies were done at six months and at yearly intervals. It was found that cardiac patients characteristically have a high degree of anxiety. Patients with advanced mitral stenosis show signs of mild cortical organicity. Mitral commissurotomy is followed by signs of generalized brain dysfunction. A certain amount of the observed deficit is reversible. Further research will be done to determine possible relationships between psychiatric symptomatology and starvation of brain tissue resulting from chronic hypoxia produced by prolonged cardiac dysfunction.—Dr. Misha S. Zaks, Northwestern University Medical School, Chicago.

• Improved technics for cultivating human cells and the newly achieved accuracy in identifying each of the 46 chromosomes in the normal diploid chromosome complement of man have opened a gateway to the possibility of demonstrating quantitative chromosomal irregularities in mental defects and disturbed patterns of sexual development.—Dr. Franz J. Kallman, New York.

TREATMENT OF WHIPPLE'S DISEASE

Southern Medical Association:

- Twelve cases of Whipple's disease, the largest reported series from one institution, have been seen at Duke Hospital since 1935. The typical clinical picture consists of diarrhea, arthralgia and lymphadenopathy; weight loss and hypotension are also common findings. Formerly, the diagnosis was made only at laparotomy or autopsy, but more recently, it has been established by peripheral lymph node or peroral intestinal biopsy. Treatment with antibiotics and adrenosteroids has been gratifying. Five patients are alive and well three months to six years after diagnosis.—Dr. W. Crockett Chears, Jr., Dallas, and Dr. Julian M. Ruffin, Durham, N. C.

- A double-blind, placebo-controlled study compared the effectiveness of the antasthmatic agent TEDRAL® with Tedral plus chlorprophenpyridamine maleate and with a placebo. The results obtained with Tedral were superior to those obtained with the placebo. However, treatment with Tedral plus the antihistamine was the most effective.—Dr. Henry Ogden, New Orleans.

- Serum chylomicron levels were found to be elevated in diabetics regardless of their state of glucose control. This may indicate that there is a primary disturbance of fat metabolism in diabetes other than the disturbance occurring as a result of inadequate utilization of glucose. This observation has led to the use of heparin to reduce lipemia. A reversal of the characteristic lesions of diabetic retinosis has been observed.—Dr. John K. Finley, Haddonfield, N. J.

GROUP PRACTICE TRIPLES IN 14 YEARS

American Association of Medical Clinics:

- A nationwide survey showed that 6.21 per cent of practicing physicians were in full-time group practice in 1959, as compared with 2.64 per cent in 1945. It is estimated that there are 1,385 groups in which three or more physicians provide services in more than one medical specialty. There were 435 such groups in 1946. About 57 per cent of the groups have from three to five full-time physicians; 24 per cent, from 6 to 10; 7.5 per cent, from 11 to 15; and 11 per cent, 16 or more.—Dr. S. David Pomrinse, United States Public Health Service, Washington, D. C.

PLACEBO LOWERS BLOOD PRESSURE

American Medical Association:

- In a double-blind study of 134 patients, injection of a placebo caused a statistically significant decrease in systolic blood pressure for 59 weeks and in diastolic blood pressure for 143 weeks. Those patients who received hydrogenated ergot alkaloids by injection had a decrease in blood pressure comparable to that obtained with injection of the placebo. Placebos administered orally three times a day did not decrease the blood pressure.—Dr. Raymond F. Grenfell, University of Mississippi School of Medicine, Jackson.

- Corneal disease is a potentiality in the six million people wearing or attempting to wear contact lenses, since very few of these persons are under medical supervision and many of the nonmedical personnel attempting to fit the lenses do not have a sound background in corneal physiology and pathology. —Dr. John W. McTigue, Washington, D. C.

- The chronically ill and disabled are not confined to the aged portion of the population. It is estimated that 26.8 per cent of the 5.3 million persons who are chronically ill are less than 45 years of age.—Dr. Paul Chodoff, Washington, D. C.

reliable absorption

consistently high peak serum levels

lethal action against the commonly encountered pneumococci, streptococci, and gonococci

lethal action also against clinical isolates of certain Staph. aureus resistant to other antibiotics

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Wyeth SERVICE TO MEDICINE

Reliable Absorption Promises Consistent Effectiveness

Numerous investigators have shown that the absorption of oral antibiotics varies not only from subject to subject, but also in the same subject at different times. To provide a high degree of therapeutic assurance, therefore, requires an antibiotic that is on the average well absorbed. High absorption, of course, implies high serum concentrations which, in turn, means an increased likelihood that tissues will be supplied with adequate antibiotic.

The absorption of phenethicillin potassium (DARCIL) has been investigated both by studies of serum concentrations and urinary excretion rates.

Maximum Absorption Indicated by Prompt, High Peak Serum Levels. Blood level studies demonstrate the reliable absorption of phenethicillin potassium. In studies employing single oral doses of 250 mg. of phenethicillin potassium, Morigi and associates[1] determined that peak serum levels of the antibiotic were attained within an hour after ingestion; assayable levels were maintained for 4 to 6 hours. Knudsen and Rolinson,[2] among others, have also demonstrated that phenethicillin potassium produces unusually high blood levels.

Serum Levels Directly Reflect Dose Levels. Cronk and associates[3] performed an interesting experiment that emphasizes the absorption of phenethicillin potassium. Phenethicillin potassium was given to healthy adults in progressively increasing doses. *The resultant serum levels were directly proportional to the doses given.*

Average Serum Concentration ½ Hr. after Administration

Dose (Mg.)	*Mcg./Ml.*	*Units/Ml.*
134	2.72	4.35
268	4.28	6.85
536	8.15	13.0
804	12.3	19.7
1072	19.1	30.6
2144	39.6	63.4

Therefore, when treating a patient with a severe infection, the physician may, by adequately increasing the dose, produce serum concentrations that should be sufficiently great to affect less susceptible pathogens.

Excellent Absorption Indicated by Urinary Excretion Studies. Knudsen and Rolinson,[2] in a study of 9 fasting subjects, reported that a mean of 60% of the dose of phenethicillin potassium was excreted in the urine within 6 hours after ingestion of the drug. Cronk and associates[3] found a lower, although still high, rate: 24 to 35% of a given dose of phenethicillin potassium was excreted in the first 6 hours; almost three-quarters of this percentage was excreted in the first 2 hours alone. Morigi and associates[1] collected urines of 10 healthy subjects at 6-hour intervals following a dose given one hour before meals. As can be seen, the excretory rate of phenethicillin potassium reflects prompt absorption and utilization.

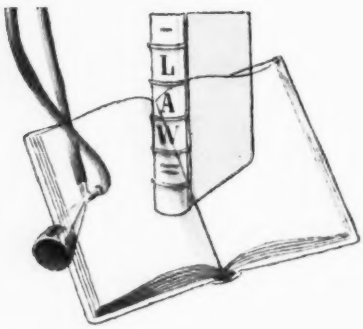
Average Urine Concentrations Following a Single Oral Dose of 250 mg. Phenethicillin Potassium

	0-6 Hrs.	*6-12 Hrs.*	*12-24 Hrs.*
phenethicillin potassium	30.9%	0.4%	0%

References: 1. Morigi, E.M.E., Wheatley, W.B., and Albright, H.: Antibiotics Ann., 1959-60, pp. 127-132. 2. Knudsen, E.T., and Rolinson, G.N.: Lancet 2:1105 (Dec. 19) 1959. 3. Cronk, G.A., Naumann, D.E., Albright, H., and Wheatley, W.B.: Antibiotics Ann., 1959-1960, pp. 133-145.

SUPPLIED: DARCIL Tablets (peach colored, scored)—250 mg. (400,000 units), 125 mg. (200,000 units) phenethicillin potassium, bottles of 36 and 100. DARCIL for Oral Solution—125 mg. (200,000 units) phenethicillin potassium per 5 cc. teaspoonful, bottle of powder to be reconstituted to 60 cc.

Although infrequent, adverse reactions to many modern drugs may occur. For further information on limitations, administration and prescribing of DARCIL, see descriptive literature or current Direction Circular.



Forensic Medicine

Mathematics of Motherhood, Part 2

MAN'S LAW OF PATERNITY VS. NATURE'S LAW OF GESTATION

IRWIN N. PERR*

Fairhill Psychiatric Hospital, Cleveland

JUST since the turn of this century the number of births has been in the billions. The United States alone has over four million births a year, the world 80 million. In a country such as ours, with fairly adequate medical recording, we have had about 100 million births since 1930. Therefore, it is reasonable to assume that pregnancy is a subject about which medical science should have vast accumulations of information.

Pregnancy occurs when the spermatozoon unites with the ovum—within 24 to 48 hours following intercourse. Within several days, the ovum becomes implanted in the uterine wall. The average woman menstruates every 28 to 30 days, although there is considerable variation. She usually ovulates about 14 days prior to the following menstrual period, so that if a woman has periods at 35 day intervals, she will ovulate nearer the twenty-first day following the onset of the preceding menses. Women with 21 day periods would ovulate nearer the seventh day. With those who are irregular, prediction is extremely difficult.

Beck[1] stated: "Although ovulation unquestionably takes place about fourteen days before the end of the menstrual cycle, the exact date of its occurrence is not known. The beginning of pregnancy, accordingly, cannot be estimated from the rather indefinite time that the egg leaves the ovary. Likewise, the date of fruitful coitus usually is unknown and therefore cannot be used in estimating the time of fertilization, and since we have no means of knowing when this event occurs, the exact length of pregnancy cannot be determined." He reports variations in pregnancy from 230 to 329 days from the beginning of the last menses.

For practical purposes, most obstetricians use the date of the last period in calculating an expected date of delivery. The most common formula is the Naegele rule, which com-

(Continued on page A-46)

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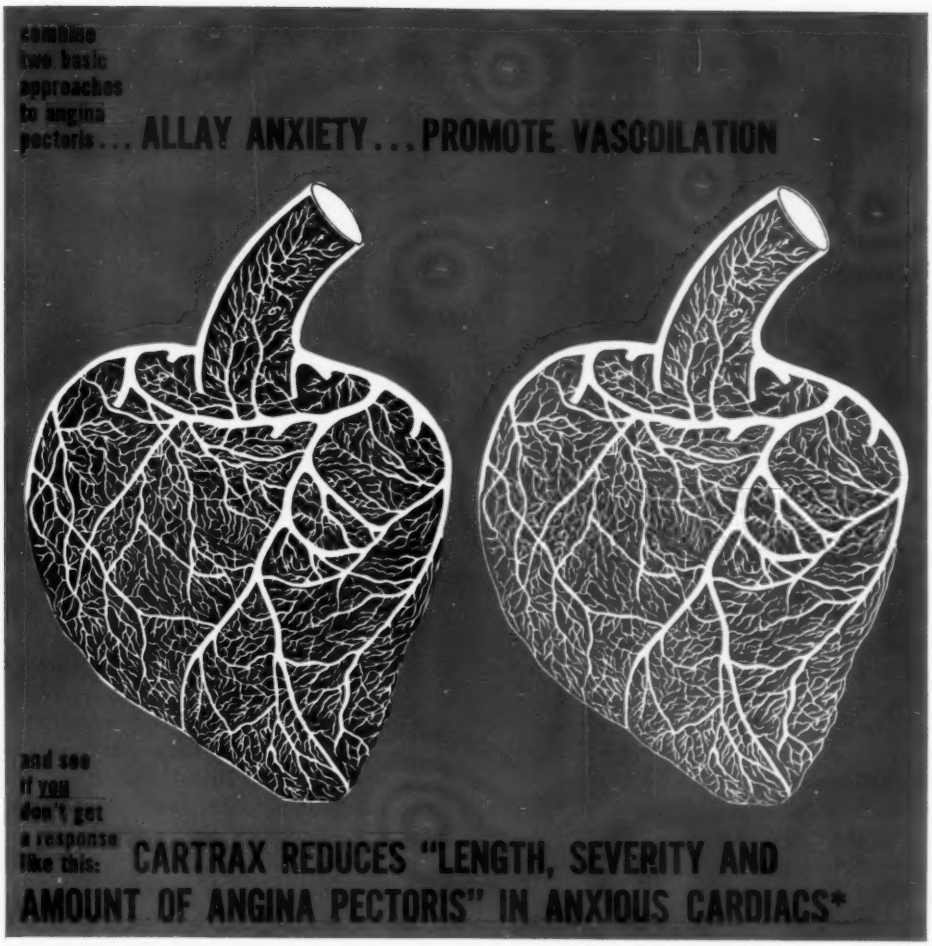
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TABLE 1*

DEVIATION FROM CALCULATED DATE OF CONFINEMENT—ACCORDING TO NAEGELE'S RULE BASED ON 4,656 BIRTHS OF MATURE INFANTS

DEVIATION IN DAYS	EARLY DELIVERY		DELIVERY ON CALCULATED DATE		LATE DELIVERY	
	Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
0			189	4.1		
1-5	860	18.5			773	16.6
6-10	610	13.1			570	12.2
11-20	733	15.7			459	9.9
21-30	211	4.5			134	2.9
31 and over	75	1.6			42	0.9

*After Eastman.

The menstrual cycles of the mothers were 28 plus or minus five days. The infants were at least 47 cm. in length and 2600 gm. in weight.

(Burger, K. and Korompai, I.: Die Bewertung der Berechnung des Geburtstermines nach Naegele auf grund unserer heutigen Kenntnisse. Zentralbl. Gynäk. 63:1290-1298, 1939.)

putes such a date by subtracting three months from such date and adding seven days. Thus, if the last normal period began on January 10, the expected date would be October 17 (or, to use numbers alone, if the last period were 6/15, then the expected date would be 3/22). This rule is very helpful as a guide, but there may be wide variations (table 1).

Using this rule, one finds that less than 1 per cent of pregnancies go beyond 300 days from the last menstrual period or about 286 days from conception. In Strand's[2] study, 2.7 per cent exceeded 301 days (using the Naegele rule in 10,151 deliveries). Burkons[3] found that in 2600 cases, 159 or 6.1 per cent exceeded 295 days from the last normal menstrual period. Nesbitt[4,5] reported that, with this rule, 25 per cent exceed 41 weeks; 10 to 12 per cent, 42 weeks; 3 to 4 per cent, 43 weeks or more. Of 7,415 pregnancies, 812 (11 per cent) lasted more than 294 days (or about 280 days from conception); this number dropped to 7.3 per cent when all of the pregnancies which were more than 20 weeks were included.

It has been found that when intervals between periods are longer than usual, the pregnancy lasts a few days longer and vice versa.[6] Higgins[7] found that in 9,277 mature pregnancies, 1.2 per cent lasted over 44 weeks and that in 57.5 per cent of his cases, delivery was accomplished in the fortieth and forty-first weeks. He stated, "Records of grossly prolonged pregnancy with a normal foetus are exceedingly rare. I have not been able to trace any reports in British literature." Walker[8] wrote, "It is notoriously difficult to be certain of the gestational age of any pregnancy when the decision has to be made after about 24 weeks, in labour, after delivery, or in any way in retrospect. In any hospital population, even with excellent systems of assessment, 18 to 20 per cent of cases have 'doubtful' dates of delivery. A good menstrual history, along with clinical assessment of uterine size before the 16th week, is the only method of establishing a clinical duration of a given pregnancy and it is at the first visit that such a decision should be made."

In any event, utilizing the Naegele rule and subtracting a reasonable time for the interval before conception, most pregnancies then average 266 to 270 days. Other means of estimating length of pregnancy are measuring the size of the abdomen or noting the date of quickening (about 22 weeks in those having a first child, or 24 weeks in those with

(Continued on page A-48)

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TABLE 2

RESULTS OF QUESTIONNAIRE ON DURATION OF PREGNANCY—39 RECEIVED

QUESTION	PREGNANCY IN DAYS										TOTAL RESPONSES
	280-289	290-299	300-309	310-319	320-329	330-339	340-349	350-359	360-369	Over 370	
1	1	4	17	6	3	3	1	1	0	0	36
2	1	2	15	4	4	3	0	1	0	0	30
3	0	0	3	3	2	2	1	3	2	2 (389)	18
4	0	3	6	6	4	1	2	3	0	1 (455)	26
5	0	5	6	0	4	2	4	4	1	1 (455)	27

previous children). These are very inaccurate yardsticks. Another means of ascertaining pregnancy is afforded by the various hormonal tests which may be positive two to four weeks after onset of pregnancy.

The various textbooks of obstetrics point out the difficulties of measurement. It is important to exclude variations due to obstetric monstrosities. For instance, anencephalic monsters may be quite delayed in time of delivery. Higgins[9] has reported a case of 389 days' duration, but such cases are noted by the physical abnormality which must be taken into account. Unable to find English cases of prolonged duration, he referred to several German cases (337 days, three cases of 321 to 338 days, 343 days with a minimum of 315 days since conception, and 360 days for an anencephalic fetus).

Related to the topic at hand is the syndrome of prolonged pregnancy or postmaturity, which is often arbitrarily measured by including all cases more than two weeks or more than three weeks beyond the expected date (depending on the author). The anatomic and physiologic features of postmaturity are not pertinent to the subject of this article, which is concerned only with the factor of duration.

The dearth of cases of prolonged pregnancy (beyond 300 days after conception) in English and American medical literature is striking. Inasmuch as pregnancy is diagnosable within the first month, one would expect reports of such cases if they occurred with any frequency.

Most of the dates mentioned were those from the last normal menstrual period—a very inaccurate gauge of pregnancy. Women do not become pregnant in relation to the period but in relation to ovulation with subsequent fertilization. Thus, if ovulation could be measured accurately, a much finer yardstick would be available. At the time of ovulation, there is a rise in body temperature; this phenomenon will be discussed further later.

Medical Opinion as Reflected in a Questionnaire

With the unsatisfactory information available, a questionnaire was designed to ascertain current medical opinion. These questionnaires were sent to the professors of obstetrics at 84 medical schools in the United States; replies were received from 39 professors. Unfortunately, the inquiry did not specify whether pregnancy was to be estimated from a likely date of conception or from the last normal menstrual period. Probably responses are based on both measurements, although more likely the latter. In either case, the variety of response is of import.

The five questions asked were:

1. In your experience, what is the longest verified pregnancy that you have encountered?

2. In your talking with fellow obstetricians, what is the longest verified pregnancy that you have heard mentioned?

3. In your reading of the literature, what is the longest verified pregnancy that you have encountered?

4. What would be your guess as to the

(Continued on page A-51)

maximal period of pregnancy possible in the human female?

5. Where do you think that courts should draw the line?

The results of this questionnaire are tabulated in table 2. Comments and explanatory notes have been omitted.

Some observations are in order. It must be stressed that the table represents a collection of opinions. Many of the letters commented that the word "verified" made dubious many of the responses, and often the difficulties in measurement were pointed out. The largest response was obtained on question 1, which was based on personal experience. The majority of opinion related to the 300 to 320 day range. On question 2, which was also based on personal experience (by hearsay), the results were basically the same. On question 3, there was much greater variability. The striking element was the sparsity of responses, less than one-half answering. This fact, plus frequent comment, made apparent the conclusion that many isolated reported cases are simply not believed. Two replies referred to the case previously reported by Higgins of an anencephalic monster. (Another defect of the study was that it did not stipulate that information was desired only about viable nonmonsters.)

The answers to questions 4 and 5 were most striking and included a wide variation of opinion, with one professor indicating that a pregnancy of 455 days was possible. Several commented that the legal problem was not to pick a number, but that each case must be evaluated in accordance with the medical information available, the types of people and the problem involved, and the utilization of all pertinent information.

To sum up the results from this small sampling:

1. About two-thirds reported pregnancies in the 300 to 319 day range. However, how many represented estimates in accordance with the Naegele rule is not shown. Many criticized this system of measurement.

2. Most do not believe published reports as to unusual periods of gestation.

3. There is a very wide range of opinion concerning the duration of pregnancy.

This study points up what has already been alluded to, namely, the failure, thus far, to accumulate scientific data, primarily because of lack of measuring tools.

Use of Basal Temperatures in Studying Length of Pregnancy

Stewart[10] has written an often-quoted article on duration of pregnancy. Having discussed the problem of measurement, he defined postmaturity as occurring in pregnancies extending 15 or more days beyond the expected date of confinement. In his study, he kept basal temperature records to indicate ovulation in 135 pregnancies. In this group, all pregnancies terminated at a date 250 to 285 days from ovulation, with an average of 266 to 270 days. One example was that of a 21 year old woman who, in her first pregnancy, menstruated on two occasions during the month preceding the last normal menstruation. A female baby, weighing 3,930 gm., was delivered 344 days later. Basal temperatures showed ovulation on the sixty-sixth day, and the duration of pregnancy from that date was 278 days. "Life was believed present at the eighteenth week from menstruation, and, as so often found in many cases of this study, is an unreliable symptom on which to base any calculations." Another pregnancy, whose length as measured from the last menstrual period was 349 days, was only 250 days as measured from ovulation.

Postmaturity among the 135 cases did not exceed three weeks. There was no evidence to support the alleged prolongation of human pregnancy to 10, 11 or 12 months, missed periods and later ovulation (or perhaps early abortion followed by a subsequent pregnancy without an intervening period) being the obvious factors. Stewart feels that the period of postmaturity is short and does not extend beyond three weeks. He commented on the 300 day limitations in Switzerland, Scotland, France and Italy, 307 days in Austria, and 302 days in Germany, feeling that they are liberal yardsticks. Stewart concluded that the maximal duration of pregnancy as deter-

(Continued on page A-52)

mined by temperature measurement of ovulation is 285 days. He feels that 300 days might be used as a reasonable limitation. "Longer periods seem most questionable and are conspicuous by the complete absence of any supporting data from this study."

Conclusions

The question of paternity and prolonged pregnancy is a common one in the courts. While many European nations stick to firm rules, English and American courts have individualized each case so that there are great variance and contradiction. In general, our courts of law favor a declaration of legitimacy where possible, and so they usually attempt to favor the woman. Thus, in all probability, there are many men in England and the United States whose only claim to paternity rests on a court's judgment.

However, while the law has fared poorly with this problem, medical science has fared no better. It is a humorous and somewhat ironic situation that we cannot delimit this problem more clearly in the face of billions of births and generations of study. Much research remains to be done. Perhaps one avenue of approach is the measurement of large numbers of pregnancies by the time of ovulation based on temperature studies. If a uniform project could be established on a widespread basis with one central reporting agency, a significant number of pregnancies and their variations could be accumulated.

Until that time or until some other yardstick is available, the present individualized method in the courts seems the appropriate way to handle these cases. Indeed, in view of the present wide range of medical opinion, there would seem to be little choice. In cases where delivery of a child takes place more than 300 days following an alleged last intercourse, the presumption of legitimacy rule should probably be eliminated, as the odds are so highly in favor of subsequent copulation. There should be supporting data of some kind in cases of indicated prolonged pregnancy, the best being the information obtained by the physician early in the pregnancy combined with continuous medical supervision.

In any event, this is one medicolegal situation where medicine and law are equally matched—and equally confused.

After innumerable milleniums of reproduction, we are in much the same position as a curious Adam might have been, had he turned to his mate and asked, "Say, Eve, how long does a pregnancy last?"

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Radiology FOR PRACTICING PHYSICIANS

Pulmonary Paragonimiasis

RAYMOND H. WATTEN*

U. S. Naval Hospital, Oakland

RAYMOND H. WATTEN

Lieutenant Commander Raymond H. Watten is a career naval medical officer currently (August 1960) assigned to the clinical research department at NAMRU-2 in Taipei, Taiwan.* He was born in Minneapolis and attended Stanford University, where he received his B.A. degree in 1946 and his M.D. degree in 1949. He interned at the U. S. Naval Hospital, Long Beach, California. During the Korean War, which interrupted his residency training in internal medicine, Dr. Watten served at the U. S. Naval Hospital, Yokosuka, Japan. On completing his residency training, he was assigned to the metabolic research unit at the U. S. Naval Hospital, Oakland. He has been at NAMRU-2 for three years, where, in addition to engaging in clinical studies of cholera and tropical diseases, he has studied the diagnosis and treatment of paragonimiasis. He also has become personally acquainted with several able Chinese parasitologists and clinicians working in this field, and he thus is particularly fitted to tell the readers of this column about pulmonary paragonimiasis.

The life cycle of the parasite *Paragonimus* is complicated, as the medical visitor to Taipei can be shown in any one of several excellent local parasitology laboratories. Lung lesions caused by this organism are all too frequently encountered in Taipei.

Because of its method of spread, paragonimiasis is most unlikely to gain a foothold in America, but it will be encountered occasionally among temporary visitors or permanent residents who have come from that part of the world.—Paul C. Hodges, M.D.†

The opinions and assertions contained herein are those of the author and are not to be construed as official or reflecting the views of the Navy Department or of the naval service at large.

*Lieutenant Commander Watten is now at the U. S. Naval Hospital, Oakland, California.

†Emeritus Professor and Chairman, Department of Radiology, University of Chicago, Chicago, Illinois.

SHORTLY after my arrival at NAMRU-2, I was given the responsibility of examining Chinese applicants seeking employment at the unit. One of these, a husky man of 48, had applied for the position of plumber. He appeared in obvious good health and his physical examination revealed nothing unusual. His chest x-ray (figure 1), however, indicated extensive pulmonary disease and I was about to reject his application when curiosity prompted me to request a sputum examination. An alert technician examined a fresh, unstained smear of the sample after finding the acid-fast stain to be negative, and reported the presence of numerous *Paragonimus* ova. The plumber got the job and became my first patient with paragonimiasis.

Further questioning of the man revealed that he was aware of his disease and had been troubled with a cough and intermittent episodes of hemoptysis. It was also learned that he was in the habit of eating raw crabs and had done so for many years, not only in Taiwan but also in his native province of Chekiang, China.

Considering the frequency of tuberculosis in Asian peoples, it is unlikely that many American physicians would consider the Oriental lung fluke as the cause of this patient's disease. Infections of this sort are sufficiently rare in the Western world to have become medical curiosities, something to be studied during medical school and vaguely remembered as interesting although useless information.

Paragonimiasis is not a medical curiosity in the Far East. In addition to frequent deaths from severe infestations, economic losses from the millions of man-hours lost each year from the effects of this disease make it a problem of international importance.

A recent item in one of Taipei's English-language newspapers indicates the disastrous consequences of *Paragonimus* infestations. A retired college professor requested medical assistance from the mayor of Taipei, stating that he and his entire family had become ill after eating uncooked river crabs four years previously. As a result of this disease, the professor's eldest son and daughter had died;

FIGURE 1. X-ray of a 48 year old NAMRU-2 employee who had eaten salted crabs for over 10 years. He had a cough with intermittent hemoptysis, and results of sputum culture were positive for *Paragonimus* ova. Otherwise, he was in good health. He had been previously treated with emetine, and he did not respond to chloroquine.

his wife was in critical condition, and effects of the disease were still present in the professor and two remaining children. The mayor promised to do what he could to get medical assistance for the unfortunate family and subsequently arranged for their hospitalization.

History and Life Cycle of Paragonimus

A study of the life cycle of the lung fluke *P. westermani* and the disease it causes in man makes one appreciate the infinite ways of nature. The fascinating and seemingly unlikely life cycle involving two intermediate hosts must have evolved only after countless modifications and adaptations. It is a tribute to many dedicated scientists that the complex interrelationships between parasite, snail, crustacean and vertebrate have been defined and the life cycle established.

Equally fascinating is the historical background of the Oriental lung fluke.[1] The first specimens were recovered from the lungs of two Bengal tigers which had died in zoos in Amsterdam and Hamburg in 1878. The first human case was discovered in Taiwan a year later by Ringer, who found a fluke at autopsy

in the lung of a Portuguese resident who had died of a ruptured aortic aneurysm. This parasite was identified as a *Distoma* fluke by Manson in Amoy, China. Later Manson found operculate eggs similar to those expressed from Ringer's fluke in the rust-tinged sputum of a Chinese patient who at one time had lived in Taiwan. About the same time, trematode eggs were found in the sputum of patients with hemoptysis in Japan; later, the mature worm was found not only in the lung but also in other parts of the body of man by pathologists in that country.

Much of the early work on the life cycle of *Paragonimus* was done by Japanese investigators working in Taiwan, Korea and Japan and later by Chinese scientists on the China mainland. Professor S. Yokogawa was for many years associated with the Tropical Disease Institute, formerly located only a few hundred yards from the present quarters of NAMRU-2 in Taipei. He contributed greatly to an understanding of the *Paragonimus* life cycle and developed an antigen from whole worm extracts which he used for skin testing and serologic studies.

The bizarre life cycle of the lung fluke (figure 2) begins when the egg, either passed in the feces or coughed up in the sputum, reaches clear, running water. After several weeks of development, a free-swimming miracidium emerges. On coming in contact with the appropriate snail host (usually of the genus *Melania*), the miracidium penetrates the soft tissues and forms a sporocyst. From the sporocyst the parasite undergoes further transition into two generations of rediae and finally develops into a cercaria, which then leaves the molluscan host and by chance becomes encysted in a fresh-water crayfish or crab (figure 3). When the appropriate host is found, the cercaria penetrates the soft parts and forms a small cyst or metacercaria, usually in the gills or muscle tissue.

Interestingly enough, massive infestation with metacercariae does not cause any apparent illness in the crab. The snail, on the other hand, may die as a result of too many miracidia encroaching on vital organs.

Studies by the department of medical zoology at NAMRU-2 have indicated that infested crabs may be found in many of the fresh-water streams in Taiwan. Several species of fresh-water crabs may carry the cysts and are the most important intermediate host, as in Taiwan crayfish are not usually eaten raw. The number of infested crabs in individual streams varies from less than 1 per cent to over 30 per cent, while the number of cysts in individual crabs averages about five. However, up to 300 cysts have been found in one crab, probably enough to cause certain death to anyone eating it.

When these raw or partially pickled crabs are eaten, the cyst is digested and the fluke emerges. Penetrating the intestinal wall, the young worm wanders around the body and usually comes to rest in the bronchioles, where it forms a cystic capsule and develops into the mature worm. The predilection of the fluke for the lungs has not been explained. The parasite does not always, however, settle in the lungs, and adult worms have been found in the eyes, lymphoid tissue, brain, kidneys, omentum, testes and subcutaneous tissue. In most extrapulmonary locations, eggs of the adult worm cannot reach the outside world, and in these cases the life cycle reaches a dead end. In the majority of *Paragonimus* infestations, however, the parasite is located in the lung, where large masses of eggs can be discharged into the tracheobronchial tree and expectorated in the typically rusty sputum. If the infested sputum is swallowed, eggs will be found in the stool.

Incidence and Cause of Paragonimiasis

Paragonimiasis is generally a disease of the Far East, with the main foci in Korea, Japan, China (mainly the coastal provinces), Taiwan and the Philippines. Instances of infestations have been reported from southeast Asia, Africa and South America. In Korea, Dr. Elvio Sadun, who until recently was associated with the 406th Army Medical General Laboratory in Japan, and Dr. A. A. Buck[2] have reported an incidence of 50 per cent in some highly endemic areas, based on the number of persons with positive reactions to a skin test with purified antigen. In Taiwan

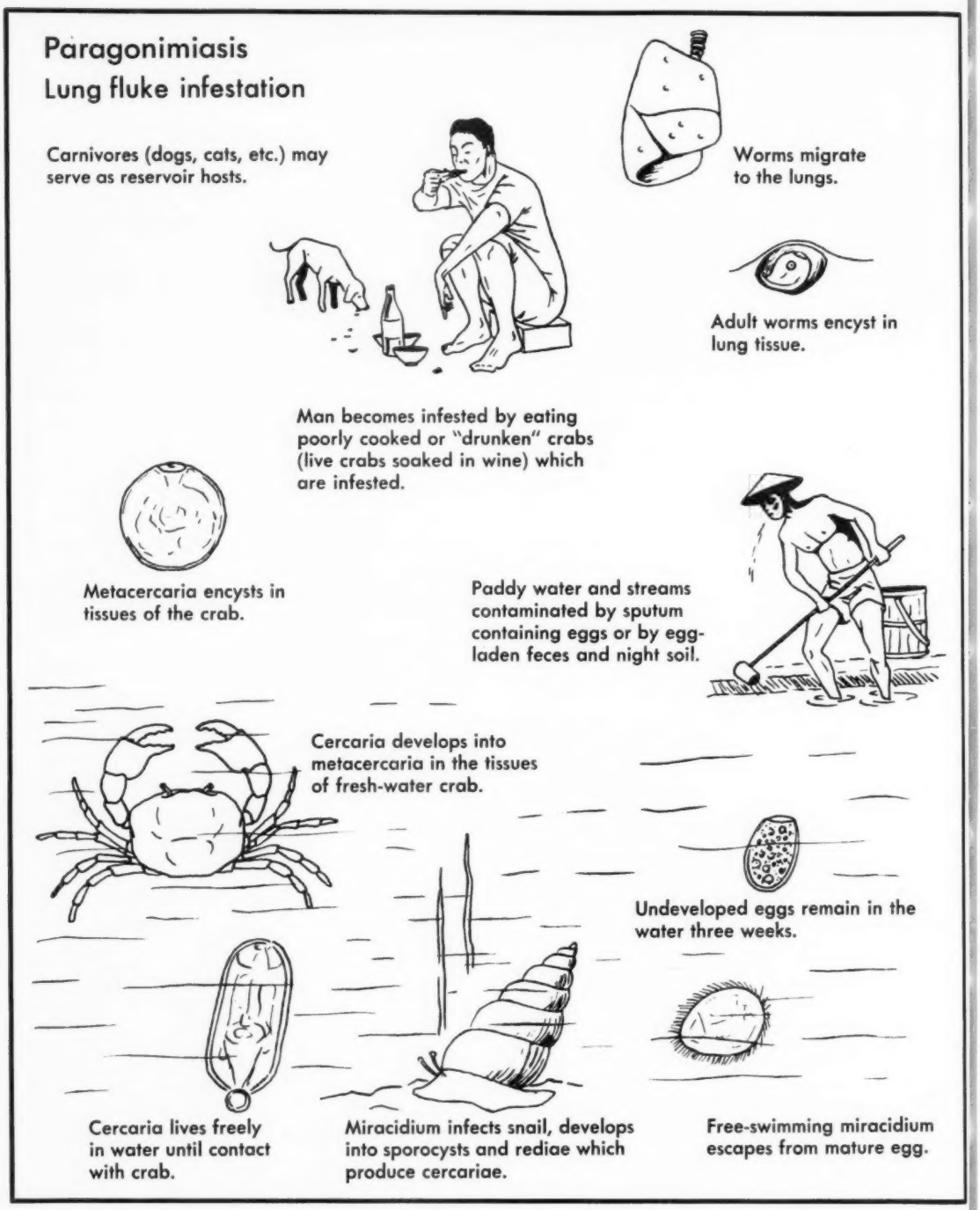
Paragonimiasis
Lung fluke infestation
Carnivores (dogs, cats, etc.) may serve as reservoir hosts.
Worms migrate to the lungs.
Adult worms encyst in lung tissue.
Man becomes infested by eating poorly cooked or "drunken" crabs (live crabs soaked in wine) which are infested.
Metacercaria encysts in tissues of the crab.
Paddy water and streams contaminated by sputum containing eggs or by egg-laden feces and night soil.
Cercaria develops into metacercaria in the tissues of fresh-water crab.
Undeveloped eggs remain in the water three weeks.
Cercaria lives freely in water until contact with crab.
Miracidium infects snail, develops into sporocysts and rediae which produce cercariae.
Free-swimming miracidium escapes from mature egg.

FIGURE 2. Life cycle of *P. westermani*.

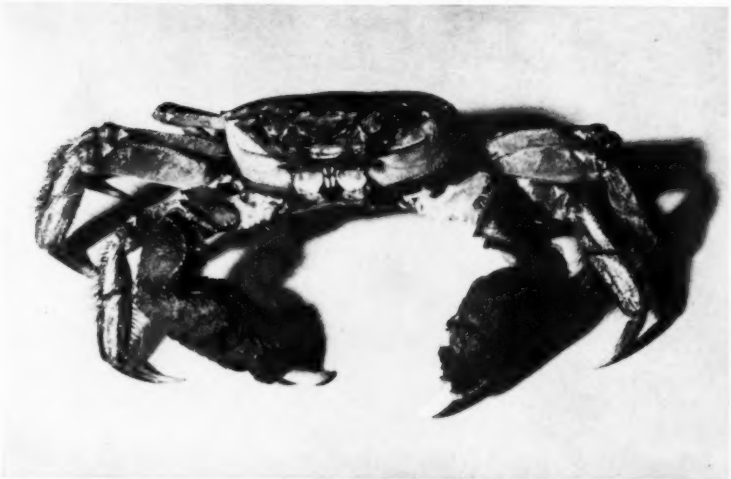

FIGURE 3. The fresh-water crab *Eriochier japonicus*, the most prevalent intermediate host for *Paragonimus* in Taiwan.

(Reproduced through the courtesy of Commander R. E. Kuntz, MSC, USN.)

an incidence of 30 per cent in known endemic areas has been found with similar skin-testing materials, but the over-all incidence is probably less than 1 per cent.[3]

Paragonimus infestations have been found in a variety of animals, including the original Bengal tiger, domestic cat, dog, pig, civet cat, mongoose and rat. Infestations in man are due to the eating of uncooked fresh-water crabs or, less commonly, crayfish infested with metacercariae. Salt-water crabs are never infested. The entire problem of paragonimiasis is related to the eating habits of Oriental peoples, many of whom prefer to eat certain fish and shellfish raw, slightly pickled or marinated in wine.

The custom of eating "drunken" crabs probably originated in Chekiang province of China, an area known for a delicious variety of homemade rice wine. Here, tradition dictates that when a girl is born to a family, a large earthen crock of the new wine is buried in the ground, to be dug up and enjoyed years later on the daughter's wedding day. This same wine is used by Chinese gourmets to anesthetize live crabs by immersion. The tender meat is sucked from the legs and body parts when the crustacean has stopped squirming.

The practice of soaking crabs in brine, soy sauce or other condiments also permits the completion of the fluke's life cycle. According to Sadun and Buck,[2] the incidence of paragonimiasis in Korea is higher in young men, as raw or pickled crabs are usually consumed with alcohol at social gatherings. Almost any exposure to heat will prevent *Paragonimus* infestations, as a temperature of 57° C. maintained for three minutes will kill the metacercariae.

Clinical Findings

Clinical findings in *Paragonimus* infestations vary greatly. From experimental studies and analyses of infestations in man resulting from a single exposure, it appears that the first symptoms of the disease become evident 8 to 15 weeks after the exposure. Symptoms are related to the area in which the parasite lodges, but usually are not severe initially. Sadun and Buck[2] noted an absence of symptoms in 20 per cent of the patients with proved paragonimiasis whom they studied in Korea; the majority of these subjects were in the younger age group with recent infections.

Pulmonary involvement with *Paragonimus* typically produces a cough intermittently productive of sputum which is red-brown in color due to the presence of blood and aggregation of eggs. Chills and fever are frequently reported, and weight loss and easy fatigability are often observed. Brain involvement is a serious and common result of *Paragonimus*

FIGURE 4. Ova of *P. westermani*.

infestation. Initial symptoms of dizziness, headache, nausea and vomiting progress to epileptic seizures, coma, hemiparesis and other manifestations of an expanding lesion in the central nervous system.

Diagnosis

There are no consistent laboratory guides other than the finding of the fluke eggs (figure 4) to aid in diagnosis. Eosinophilia is often noted and together with leukocytosis is prominent during the first few months of an infestation. In areas where paragonimiasis is endemic, other parasites also are prevalent, so the finding of eosinophilia is rarely helpful.

The natural history of paragonimiasis in man is variable and not fully understood. The life span of the parasite is estimated to be about 10 years, but some reports indicate that the fluke may live as long as 20 years. Mortality and morbidity figures on paragonimiasis are generally lacking, but indirect evidence that infestation with the lung fluke is dangerous has been offered by the results of skin-testing programs in South Korea by Sadun and Buck.[2] Their corrected data showed a decrease in the number of persons who had positive dermal reactions after age 35. They postulated that a large portion of individuals with paragonimiasis, especially those with the more serious extrapulmonary infestations, will die from the disease or complications resulting from it.

Immunochemical methods for detecting paragonimiasis, including skin tests and serologic tests, have been under intensive study by Sadun and Buck.[2] Crude extracts of whole worms had previously been used by Yokogawa in surveys conducted in Taiwan and Japan. One problem he encountered was lack of specificity due to cross reactions with related trematodes such as *Clonorchis sinensis*. Sadun and Buck[2] prepared a purified antigen, using the acid extraction method of Melchers, who developed the *Trichinella* skin test antigen. Preliminary testing of this material on patients with proved paragonimiasis showed that a positive dermal reaction was produced in all cases, while in a control group there were three false positive reactions in 91 subjects. Further testing indicated that cross reactions with *Clonorchis* antigens did occur but were easily differentiated by the size of the reactions. Field studies of over 3000 subjects in Korea indicated that the antigen material was useful and had a high degree of specificity. Eggs of *Paragonimus* were detected in single sputum specimens of 40 per cent of the persons with positive reactions. These antigens are still under investigation and have not yet

FIGURE 5. X-ray of a 34 year old man who had eaten uncooked crabs in China and Taiwan for 15 years. He had had onset of cough, hemoptysis, chills and fever 10 months before this x-ray was taken. Results of sputum culture were positive for *Paragonimus* ova. Treatment with chloroquine did not prove effective.

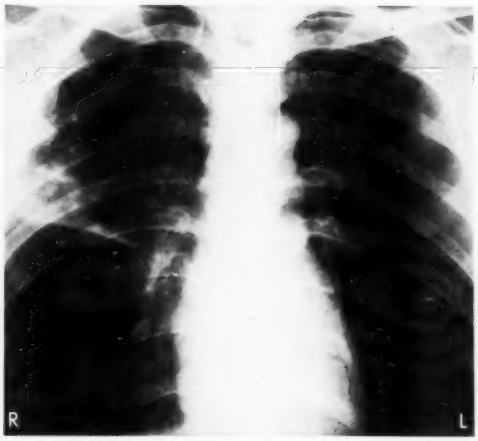

FIGURE 6. X-ray of a 39 year old man who had eaten uncooked crabs for over 10 years. He had had cough and hemoptysis for six years, and tuberculosis (for which he was treated) had been diagnosed. Sputum culture showed heavy infestation of *Paragonimus* ova. He had received no treatment for paragonimiasis.

been made available for general use.

Our experiences[3] using Sadun and Buck's antigen in Taiwan yielded similar results except for recovery of the *Paragonimus* ova. Whereas in their study the majority of egg isolations were made from sputum, over 90 per cent of our isolations were from stool specimens. Whatever the reason for the difference in recovery of the ova, the important fact is that *Paragonimus* eggs may be recovered from either sputum or fecal specimens.

It may be argued that the presence of ova in the stool is not dependable evidence that a suspected pulmonary lesion is paragonimiasis. However, extrapulmonary lesions due to *Paragonimus* have no means of access to the alimentary tract; hence, the finding of ova in the stool may be accepted as definite evidence of a pulmonary infestation.

Sadun and Buck[2] admit that a positive result in a skin test is not unequivocal evidence of infestation. The finding of eggs in sputum or feces requires patience, experience and persistence. In a group of patients who had positive reactions to skin tests and x-ray evidence of pulmonary involvement, repeated examinations of sputum and stool specimens resulted in the finding of eggs in only 80 per cent. In one patient, 27 specimens were examined before the diagnosis was confirmed.

Failure to recover eggs from all patients who have positive reactions to skin tests may be due to extrapulmonary involvement or lack of communication between the parasitic cyst and the bronchioles. In addition, the fluke normally ovulates at irregular intervals, and there is evidence that dermal sensitivity to *Paragonimus* antigen may persist after death of the fluke. False positive reactions also will occur in a small percentage of individuals in whom no evidence of infestation can be found.

The roentgenologic diagnosis of pulmonary paragonimiasis is difficult even for experienced radiologists, as the full-blown disease resembles tuberculosis so closely on x-ray that many patients with paragonimiasis are being treated in sanatoriums for a nonexistent acid-fast infection. Unfortunately, methods of staining sputum samples for *Mycobacterium tuberculosis* distort or destroy the *Paragonimus* ova, so the accidental finding of the characteristic fluke egg is rarely possible by this means.

A recent article by Professor Yang and associates,[4] of the National Taiwan University Hospital, Taipei, outlined the clinical and roentgenologic course of pulmonary paragoni-

FIGURE 7. X-ray of a 16 year old boy who had eaten uncooked crabs in Taiwan for several years. He had had cough and hemoptysis for two years, and the sputum culture showed *Paragonimus* ova. This patient was unable to tolerate chloroquine. His mother and father also had paragonimiasis.

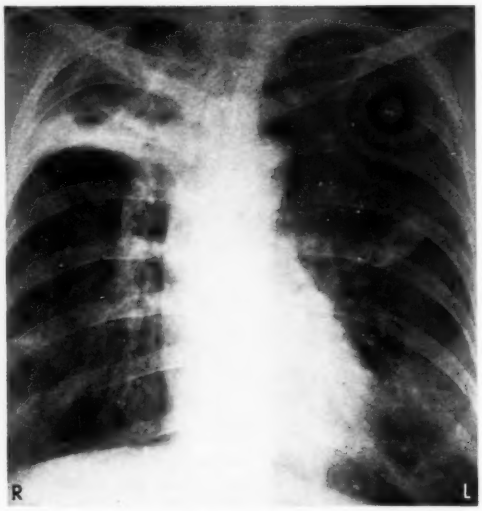

FIGURE 8. X-ray of a 45 year old woman who had had cough, hemoptysis and weight loss of two years' duration. She had eaten uncooked crabs for 11 years. Results of sputum culture were positive for *Paragonimus* ova and acid-fast bacilli.

miasis based on observations of over 300 proved cases, some of which were followed for more than 10 years. They divided the course and x-ray findings of the disease into three phases: the stage of migrating larvae, the stage of mature worms, and the stage of recovery. In the first stage, x-ray findings include pleurisy, with or without effusion, and usually bilateral, which may be accompanied by either spontaneous pneumothorax or a soft pulmonary infiltration. The second stage is characterized by the finding of well-defined patches or nodules having small translucent centers, the so-called cystic nodules (figures 5 and 6). These lesions are best seen by sectional radiography and are perhaps as typical of paragonimiasis as is any other radiologic sign. The stage of recovery is typified by fibrotic to calcified densities which have replaced the cystic nodules (figure 7). The presence of calcium in these lesions is, as claimed by these investigators, definite evidence that the worm has died. Paragonimiasis and tuberculosis may coexist (figure 8), and such instances are by no means rare.

Sadun and Buck,[2] in reporting on 140 closely followed patients with pulmonary paragonimiasis, used a classification similar to that of Yang and associates[4] and stressed the value of sectional radiography. They also noted, as have other investigators, that the second-stage cystic nodules are rarely found in the apical region.

Treatment

There is no specific drug therapy for paragonimiasis as yet. The treatment of choice among physicians in Asia has been emetine. Yang and associates[4] urge its use even though they state that the effect is only "symptomatic and temporary." Disappearance of eggs from the sputum and diminution of sputum and hemoptysis will occur following a course of emetine, but relapse invariably occurs in a few months. The repeated use of emetine, particularly when given intravenously (as is often the case in Taiwan), is hazardous. I have seen electrocardiographic evidence of myocardial damage in patients recently treated with this drug and am aware of many instances in which repeated courses have been unsuccessful in treating paragonimiasis. In view of the known toxicity of emetine and the poor results it affords, there seems to be

FIGURE 9. Skin test with purified antigen of *P. westermani* being performed on a farm woman in a small village in central Taiwan.

little justification for its continued use. Surgical resection of involved lung segments has not been employed routinely. This approach, although heroic, should bring about a permanent cure.

Chloroquine phosphate has been used during the past decade, first by Chung, Chien and Hoh[5] in China and then by others, for sporadic cases. Sadun and Buck, working at the German Red Cross Hospital, Korea, used this drug in treating 116 patients with paragonimiasis. Their results, based on follow-up examinations at regular intervals after treatment, showed that at completion of treatment half the patients showed negative results of sputum and stool examinations, but six months later only 12.5 per cent of the patients treated could be judged as cured. They commented that a total dosage of 40 gm. (1 gm. daily) seemed to be maximally effective, and that patients with recent infections seemed to respond more readily than those with long-standing disease.

Comment

Research studies designed to increase our knowledge of the biology, epidemiology, diagnosis and treatment of paragonimiasis are in progress in several areas of the Far East. NAMRU-2 has an ambitious program of studies in the fields of clinical investigation and medical zoology, including the testing of new drugs and evaluating methods of diagnosis (figure 9). In time the accumulation of knowledge from these efforts will solve the many problems related to control of the Oriental lung fluke. These problems would cease to exist, of course, if the people would always cook fresh-water crabs and crayfish before they ate them.

Conclusions

1. In the light of present-day knowledge, human paragonimiasis can be acquired only by ingesting raw or uncooked fresh-water crabs that harbor the parasite in its cystic form. The *Paragonimus* eggs occasionally shed in a patient's sputum or stool are not infectious for humans.

2. *Paragonimus* eggs are not always present in the sputum in known cases of paragonimiasis, and even if present they are apt to be destroyed by procedures regularly employed to demonstrate *Myco. tuberculosis.*

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3. The finding of eggs in the stool of a patient suspected of having pulmonary paragonimiasis is highly diagnostic, because only when flukes are in the lungs are their eggs able to reach the alimentary tract.

4. No specific therapy for paragonimiasis is known.

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AUSTRALIA

Endemic goiter—In the *Medical Journal of Australia*, Dr. H. B. Gibson, Mr. J. F. Howeler and Dr. F. W. Clements have discussed seasonal epidemics of endemic goiter in Tasmania, where this condition has been prevalent for many years.

In 1954 it was observed that in some areas endemic goiter occurred in spite of the prophylactic use of 10 mg. potassium iodide tablets by all school children. In 1956, routine medical inspection at the primary school at Margate revealed an unusually high incidence of goiter. The records of many individual children showed that the thyroid gland had visibly enlarged over a period of one or two years. Similar observations were made in larger schools at Snug and Woodbridge.

The authors believe that a food goitrogen may be responsible for the incidence of endemic goiter in these areas. The highest incidence appears to coincide with the spring growth of pastures and weeds. It is hypothesized that a goitrogen present in the fodder of cattle is later ingested in milk by the populace.

Skin infections caused by fungi—Dr. Mary Morton, University of Melbourne, has conducted investigations to determine the percentage of skin infections caused by fungi and to classify the types of pathogenic fungi involved.

Two independent surveys were conducted. One survey covered a period of two weeks in May 1958 and involved 125 patients who were being treated by dermatologists for various skin complaints. Scrapings were obtained from 67 patients; the remaining 58 evidenced no clinical signs of lesions caused by fungi. The other investigation covered the period from December 1957 to June 1959 and was concerned with 451 patients who were referred to Dr. Morton by dermatologists. All these patients had skin conditions which were clinically attributed to fungous infections.

Laboratory tests were carried out on these patients, and the positive findings were classified mycologically. An analysis of the types of fungi infecting various anatomic areas was made. Dr. Morton stated that *Microsporum canis* was most frequently isolated from the head and body, *Trichophyton rubrum* from the feet and nails, *Epidermophyton floccosum* from the groin, and *Candida albicans* from mucous membranes. Hair infections caused by *M. audouini* (dysgonic type), *T. schoenleini, T. violaceum* and *T. sulfureum* also were encountered. Several cases of "cattle ringworm" were seen.

Dr. Morton pointed out the inadequacy of Wood's light as a tool for diagnosing endothrix

(Continued on page A-78)

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tinea capitis and emphasized the need for accurate mycologic examination.

AUSTRIA

Epidemic keratoconjunctivitis—In a lecture to the Society of Physicians in Vienna, G. Zehetbauer reported that about 60 patients with epidemic keratoconjunctivitis were seen at the second ophthalmologic clinic of the University of Vienna during the winter months of 1957 and 1958. Many of these patients did not return for postepidemic checkups; however, the disease was followed in 23 patients.

The disease started with a typical hyperemic catarrh, frequently with concomitant enlargement of the preauricular lymph nodes. Complications such as diphtheritic membranous coatings or hemorrhages beneath the conjunctiva were not seen. Both eyes were affected simultaneously only when both had been previously injured. In all but two patients, both eyes were altered by the disease. Nineteen of the 23 patients had typical corneal small foci, and two of these still had trouble two years later as a result of corneal scars. Since there is no effective treatment for this condition, prevention must be stressed.

C. Kunz recalled that in 1955 Jawetz isolated adenovirus type 8 from patients with epidemic keratoconjunctivitis. His results encouraged the making of virologic and serologic studies on the Viennese patients. By transferring the secretion from the conjunctiva to cultures of cellular tissue, three viral strains were cultivated from 21 patients. Jawetz identified two of the strains as adenovirus type 8. Further research by Kunz indicated that the third viral strain also was characteristic of adenovirus type 8. In 14 cases, serologic investigations, made with two specimens of serum each time, demonstrated on seven occasions a diagnostically significant increase in the titer of the neutralizing antibodies. The combined results of the virologic and serologic tests showed that the condition was caused by adenovirus type 8 in at least eight patients.

Lindner said that during the time of Fuchs epidemic keratoconjunctivitis was called congestive catarrh and could not be differentiated clinically from trachoma until it had progressed. Only after the discovery of trachoma bodies by Prowazek did it become possible to differentiate these conditions at the onset. Lindner also mentioned that almost none of the patients observed in this study wore glasses, and that infection can develop without injury to the cornea.

A. Pillar stated that cocainization of the conjunctival sac promotes the start of the infection, since cocaine and its derivatives are harmful to the epithelium of the conjunctiva. J. Boeck noted that the infection has occurred after the use of Novesin anesthesia and after instillation of a boric acid solution or physiologic saline. In such cases, the virus is evidently transmitted by a contaminated instillator.

Much recalled that no antibiotics were available in the 1938 epidemic. At that time, intramuscular and especially intracutaneous injections of the patient's own blood, in addition to mild topical treatment, mitigated the symptoms. In a later epidemic, intracutaneous injection of bee's venom as an adjuvant was even more effective.

In conclusion, Zehetbauer stated that no specific therapy for keratoconjunctivitis is known at this time, but therapy that will increase the body's general resistance is indicated.

BRAZIL

"Familial amyloidotic polyneuropathy"—In *O Hospital,* E. Mac-Clure, A. Raick, O. Lemos and C. S. Ferreira have reported on an atypical case of primary amyloidosis of the peripheral nervous system. In this patient, a Portuguese, the disease began with paresthetic disturbances of the lower limbs and digestive symptomatology, followed by polyneuritis resulting in both paralysis of the lower limbs and muscular atrophy. The patient's father and two cousins had had similar lesions.

Examination at autopsy showed deposits of amyloid extending throughout the peripheral nerves and particularly the endoneurium, with degenerative lesions of the nerve fibers which were caused partly by ischemia and partly by compression. Smaller deposits of amyloid were found in the vascular system and in the connective tissue of some organs.

(Continued on page A-80)

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Dihydrostreptomycin in treatment of pulmonary tuberculosis—In *Publicações médicas*, F. Fonseca e Silva and J. B. F. Alhais have presented the results of a study of 29 patients with pulmonary tuberculosis who were treated with a drug containing 20 per cent dihydrostreptomycin pantothenate and 80 per cent dihydrostreptomycin sulfate. All the patients had discontinued using streptomycin previously because of intolerance to the drug.

During a five month period, dihydrostreptomycin was administered to these patients in a dosage of 1 gm. daily for 30 days followed by 1 gm. every other day for 123 days, together with 600 mg. INH® daily. Use of this drug did not alter the auditory acuity in 16 patients who had audiograms. Eleven patients did not have audiograms because transmission deafness already was present. Five of seven patients who had disturbances of equilibrium showed improvement after receiving dihydrostreptomycin; in three of them the improvement was permanent, and in two it was followed by a relapse. Three other patients had disturbances of equilibrium which were not present before treatment with dihydrostreptomycin was begun; however, in these patients, complications developed.

Several of the symptoms which had been caused by streptomycin, such as numbness, headaches, tremor, facial nerve reactions, trismus and paresthesias, regressed, improved or cleared completely after treatment with dihydrostreptomycin.

ENGLAND

Premedication with orally administered atropine — Although atropine has been used therapeutically since 1873, it was not until after 1890 that the subcutaneous injection of atropine before induction of anesthesia (to prevent excessive salivation with ether) came into general use. There seems to be no record of the oral administration of atropine before operation, and even when sedatives have been given by mouth preoperatively, it has still been common practice to inject atropine.

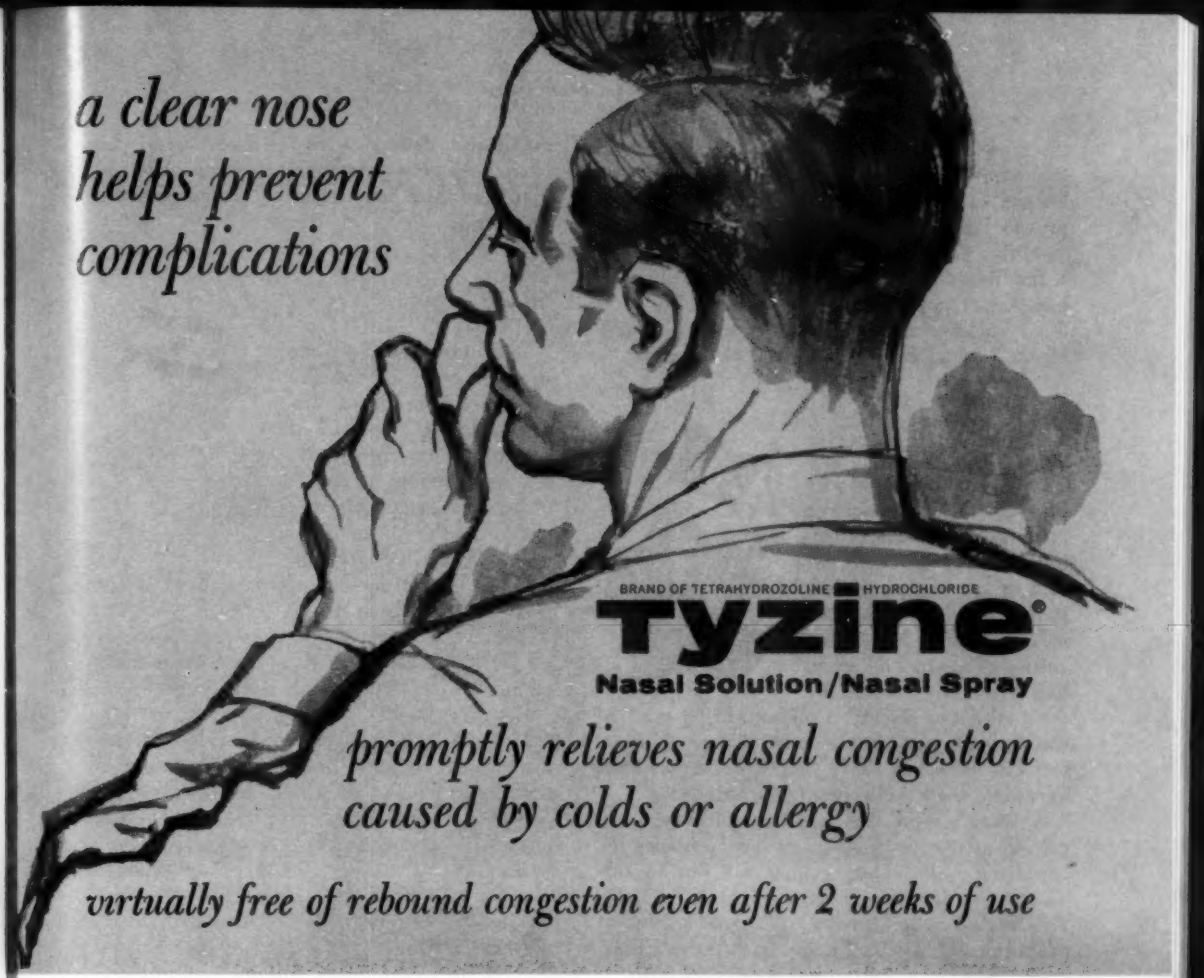
Dr. M. C. Joseph, department of child health, and Dr. R. J. Vale, consultant anesthetist, Guy's Hospital, London, have carried out a trial of premedication with orally administered atropine, and have reported their conclusions in the *Lancet*. At the Evelina Hospital, London, 147 children who underwent tonsillectomy under the same surgeon and anesthetist were randomly selected for oral or subcutaneous administration of atropine before induction of anesthesia. The anesthetist was unaware of the grouping.

During the night before operation the pulse of the sleeping child was measured twice. The next morning, an hour before the expected time of operation, atropine was given (either 0.85 mg. orally or 0.64 mg. subcutaneously), together with butobarbitone in a dose of 75 mg. per stone (14 lb.) of body weight. The average time between giving atropine and inducing anesthesia was between 87 and 95 minutes. The size of the pupils was measured to the nearest millimeter in the anesthetic room. Ether was used in all patients after anesthesia was induced with either ethyl chloride or nitrous oxide and oxygen. The anesthetist assessed the degree of salivation during induction by inserting a finger into the buccal sulcus.

The authors were unable to show that the size of the pupils, rise in pulse rate, and salivation were related. The effects on salivation, pupils, pulse rate and anesthesia were carefully observed, and no differences between the groups of children were found. It is concluded therefore that orally administered atropine is satisfactory for preanesthesia medication in children.

Myasthenia gravis—a new hypothesis—Dr. John A. Simpson, neurology unit, University of Edinburgh Faculty of Medicine, has recently published in the *Scottish Medical Journal* an analysis of 440 cases of myasthenia gravis, and has come to some interesting conclusions. He suggests that myasthenia is an "autoimmune" response of muscle in which an antibody to end-plate protein may be formed. This would have the properties of an acetylcholine-competitive-blocking substance specific to the individual and occasionally to the fetus of a myasthenic mother. Nerve endings, muscle fibers and, on occasion, the central nervous system might sometimes be involved, in close analogy with diffuse lupus erythematosus and dermatomyositis. Myasthenia gravis is, therefore, a restricted form of myositis. It may be the result of an autoimmune response to infection, usually of the upper respiratory tract; or the reticuloendothelial system, specifically the thymus, may react to end-plate protein of

(Continued on page A-82)



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INDICATIONS: Relieves inflammatory hyperemia and edema of the nasal mucosa and congestive obstruction of sinus and eustachian ostia, as may occur in the common cold, hay fever, perennial vasomotor rhinitis, chronic hypertrophic rhinitis, and sinusitis.

DOSAGE AND ADMINISTRATION: Adults and Children 6 Years and Over—2 to 4 drops of TYZINE (0.1%) in each nostril as needed, not more often than every three hours. When using TYZINE Nasal Spray, insert tip of plastic bottle into nostril, tilt the head slightly forward from an upright position, and squeeze sharply 3 or 4 times, not more often than every three hours.

Important: Use TYZINE Pediatric Nasal Drops (0.05%) for children under 6 years. The 0.1% concentration is contraindicated in this age group.

SIDE EFFECTS: Transient mild local irritation after instillation has been reported in rare instances.

PRECAUTIONS: Avoid doses greater or more frequent than those recommended above. Use with caution in hypertensive and hyperthyroid patients.

Overdosage may cause drowsiness, deep sleep, and, rarely, marked hypotension in infants and young children. KEEP OUT OF HANDS OF CHILDREN OF ALL AGES.

SUPPLIED: *Nasal Solution,* 1-oz. dropper bottles, 0.1%. *Nasal Spray,* 15 cc., in plastic bottles, 0.1%. *Pediatric Nasal Drops,* ½-oz. bottles, 0.05%, with *calibrated* dropper.

More detailed professional information available on request.

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the muscle as if it were foreign in disorders of the thymus. The latter is probably under the influence of the pituitary gland, probably by a growth hormone, and this may be a necessary condition for the allergic response to infection. A familial incidence of thyrotoxicosis or diabetes has been reported for the first time. No other theory of myasthenia gravis attempts to explain all the clinical and experimental phenomena.

FRANCE

Polyneuritis—The polyneuritis which occurred in thousands of Moroccans in 1959 as a result of triorthocresyl phosphate poisoning has been described in a number of articles. Ingestion of cooking oil which had been adulterated by the addition of discarded oil used in jet aviation was determined to be the cause of the poisoning. In *La Presse médicale,* H. Geoffroy and associates have described this type of poisoning.

A latent period of 8 to 35 days following ingestion of triorthocresyl phosphate precedes the appearance of definite symptoms; during this time the patient may have a slight indigestion. This period is followed by the development of profuse nasal discharge, lacrimation and diarrhea. Cramps in the lower extremities precede by a few hours the onset of lameness, which begins in the feet and moves upward throughout the lower limbs. In one-third of patients, paralysis may ascend as far as the psoas muscles by the tenth to the twelfth day. At this time, the upper extremities become affected, with the paralysis beginning in the muscles of the hand and moving upward toward the shoulder girdle. Muscles of the head and trunk are never affected.

Paralysis is accompanied by a diminution or total loss of sensation and sometimes by a loss of thermal perception in the paralyzed areas. These areas are bluish and cold to the touch but are not moist, due to a lack of perspiration. Improvement begins after a period of three months, but only one-third of the patients attain full recovery. In the remainder, a spastic condition persists.

Daily injections of 20 mg. pilocarpine have proved helpful in this condition. Re-education of the patient also is most important. In regard to survival, the prognosis in triorthocresyl phosphate poisoning is favorable, but adequate function is restored only when no contractures have developed.

SPAIN

Gynecologic Society meeting—Some of the gynecologic problems discussed during a meeting of Spanish gynecologists in Madrid were the influence of the social factor and obstetric methods on perinatal mortality, benign pathologic conditions of the cervix, and obstruction of the fallopian tubes.

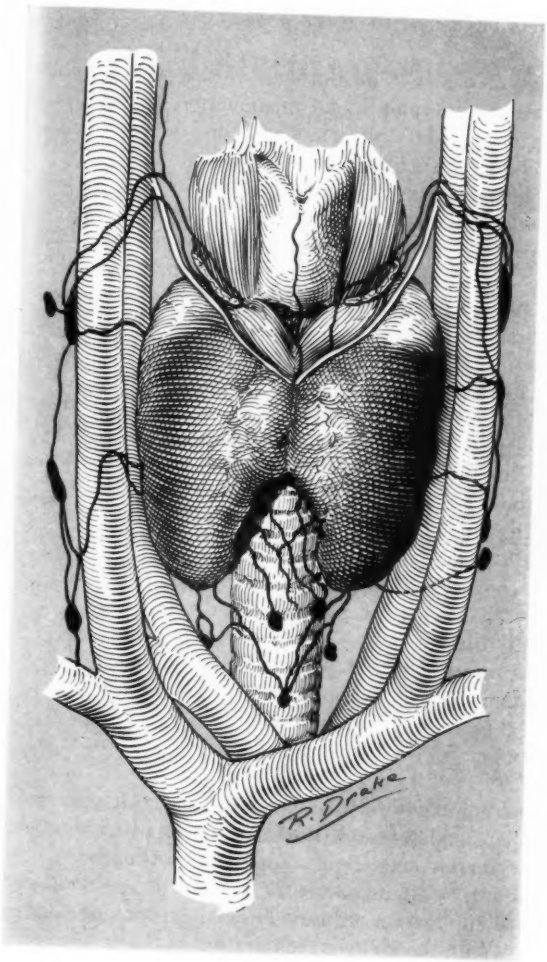
Because of improved medical assistance and proper use of antibiotics, the maternal mortality in Spain is less than one in 1000. However, the perinatal mortality is high (from 5 to 6 per cent). This is due in part to the fact that many births occur either in the home, often with general practitioners, midwives or even untrained persons the only attendants, or in poorly equipped medical institutions. The consensus is that it would be better to have a few large, well-equipped maternity hospitals than to have many small, inadequately equipped ones. Medical services at the maternity hospitals should include a doctor in charge, three or four trained medical assistants, midwives, nurses, a puericulturist, and a neonatal surgeon; equipment for blood transfusions and resuscitation should be available. An unfavorable effect on fetal life also has been noted if the mother is more than 30 years old when her first child is born.

In the discussion on benign pathologic conditions of the cervix, it was pointed out that many lesions of the neck of the cervix, or so-called cancer *in situ*, are on the border line between benign and degenerative processes. While these lesions appear benign, they can cause death if improperly diagnosed and treated. The development of cancer in many cases can be prevented by proper diagnosis and treatment.

The gynecologists also stated that obstruction of the fallopian tubes is one of the principal causes, if not the main cause, of sterility. Basic causes of obstruction of the fallopian tubes are endometritis, inflammations and infections (particularly tuberculous infections).

Postgraduate
Medicine

SPECIAL ISSUE



Endocrinology

JANUARY 1961

INTRODUCTION

THIS special issue of POSTGRADUATE MEDICINE deals with disturbances of endocrine glands, as well as with normal physiologic and biochemical aspects of these glands. There has been a tremendous amount of progress in unraveling the complexities of the function and interrelationships of the various glands. The exciting new developments in genetics, protein and enzyme chemistry, and metabolic interrelationships should be a challenge to every physician.

Several quotations from the writings of Fuller Albright, one of the world's most renowned endocrinologists, will serve admirably as an introduction to this symposium. "The physician who calls himself an endocrinologist and confines his interest to such unfortunate members of society as might appear in the side show of a circus never realizes that pneumonia, a broken leg and a bad burn involve important changes in adrenal cortical function (cf. 'alarm reaction' of Selye), that the disturbance in homeostasis occasioned by chronic renal insufficiency is ameliorated by a secondary hyperparathyroidism (and sometimes made worse), that the somatotropic action of testosterone propionate may be made use of in many conditions other than male hypogonadism, and so on . . . . What endocrinology is not . . . . First in order of frequency comes the fat boy who is slightly late in sexual development and whose genitalia are obscured by excess of fat . . . . The author is frequently asked, in giving a talk, to make it 'practical' and not too 'theoretical.' By 'practical' is usually meant 'therapeutic;' by 'theoretical' is meant 'fundamental.' The author has no patience with such a philosophy. One cannot possibly practice good medicine and not understand the fundamentals underlying therapy."

Albright's philosophy as expressed above should be a cornerstone for all of our teaching and learning of medicine. As he implies, all disease processes ultimately must be understood as metabolic disturbances—disturbances of protein, lipid and carbohydrate chemistry. The explanation of pathogenicity of microorganisms rests in their individual chemical and metabolic properties. Pause for just a moment to contemplate the fact that so commonplace a symptom as fever really has not been explained.

It is a real pleasure to introduce the contributors in this symposium. All of them are outstanding physicians, teachers and research workers. The approach to the topic each discusses is along the fundamental lines about which Albright has written. Some of the papers deal only with fundamental aspects of endocrinology, but all others deal with the application of fundamental knowledge to diagnostic and therapeutic problems. With the modern technics discussed, it is possible to be very precise in both diagnosis and treatment.

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Sex Chromatin and Chromosomes in Man

D. J. PATANELLI AND W. O. NELSON*

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Recent developments in experimental embryology, discovery of the sex chromatin, and improved methods of study in the field of cytogenetics have led to advances in the determination of genetic sex in man. These studies also offer new avenues of clinical applications in cases involving human intersexual conditions.

While information already available has exciting implications, the authors caution that continuing progress in this field will undoubtedly lead to modifications in interpretations and in significance of some of the current findings.

D. J. PATANELLI

W. O. NELSON

Sex Chromatin Patterns

FOR many years scientists have sought a method for the ready determination of genetic sex in man. Laborious procedures, including examination of meiotic divisions of gametocytes, scarcely provided a suitable answer to this problem. However, in the course of studying the nuclear morphology of neural cells in the cat, Barr and his associates[1,2] discovered a previously unrecognized sexual dimorphism that permitted identification of tissue as being of male or female origin. When this study was extended to other forms, it was possible to identify female tissue in many instances, including man, by the presence of a characteristic chromatin mass. This mass is absent or only occasionally seen in male cells. Table 1 gives a summary of a group of normal males and females studied by this method.

The sex chromatin mass that characterizes nuclei in human females is usually adherent to the inner surface of the nuclear membrane and often is so closely related to the membrane as to have a planoconvex outline.[3] It is about 1 μ in diameter and can be resolved frequently into two components of equal size. The sex chromatin shares with the

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GLOSSARY

TERM	DEFINITION
Acrocentric chromosomes	Chromosomes which are rodlike, having one arm very small or even imperceptible.
Allocyclic	See definition of "heterochromatic."
Autosomes	The chromosomes exclusive of the sex chromosomes.
Chromatin	The material in chromosomes (desoxyribonucleic acid).
Chromocenter	Mass of associated centromere regions of all chromosomes.
Diploid	Having double the basic or haploid number of chromosomes for the species, the full set of homologous chromosomes (46 in man).
Euchromatic	Faintly staining or nonstaining chromosome sections.
Feulgen-positive	Staining procedure for chromosomes; specifically indicating the presence of DNA (desoxyribonucleic acid).
Gametocytes	Either one of the sex cells, eggs or spermatozoa.
Gametogenesis	Formation of either spermatozoa or egg cells.
Haploid	Each chromosome represented singly; the number of chromosomes in the mature egg or sperm (23 in man).
Heterochromatic	Chromosomes or portions of the chromosomes during interphase (between divisions) which stain differently from the remainder of the chromosomes. This may reveal itself as heteropyknosis (dark-staining) or allocycly (lighter-staining).
Heterogametic	Having an unlike pair of sex chromosomes, e.g., XY.
Heteroploidy	Changes involving the numbers of chromosomes in a set.
Homologous chromosomes	Corresponding chromosomes that make up a pair.
Interphase nuclei	Stage in which the cell is not actively dividing. Chromosomes are usually not distinguishable.
Inversion	Rotation of a block of genes within a chromosome.
Isochromatic	Having the same staining qualities.
Meiosis	A process that consists of two consecutive cell divisions. In the first division, the homologous chromosomes separate; in the second, the chromosomes which have already duplicated themselves separate.
Metaphase	Stage of mitosis at which the chromosomes are arranged in a single plane, about midway between the two poles of the spindle, to form an equatorial plate.
Mitosis	Process of nuclear division during which chromosomes split longitudinally and a half goes to each of the daughter nuclei. Prior to splitting, the chromosomes replicate themselves; it is these double chromosomes that split.
Nondisjunction	Both homologous chromosomes (sex or autosomes) migrate to one pole of the spindle during one of the two meiotic anaphases, leaving the other pole without a representative of the pair.
Phenotype	Appearance of the organism, the sum total of all its characteristics.
Polyploid	Having some multiple greater than twice the basic haploid number of chromosomes present in each cell.
Prophase	The stage in which, as a cell is preparing to divide, the chromosomes become clearly visible as stainable threads that gradually shorten and thicken by means of coiling or spiralization.
Sex-linked	Inheritable traits borne on the sex chromosomes.
Somatic pairing	Homologous members of each pair of chromosomes tend to be side by side in the cell nuclei.
Translocation	Exchange of parts between nonhomologous chromosomes to form two new chromosomes.
Trisomic	Addition of one chromosome to one set = $2n + 1$.
Zygote	Cell formed by fusion of two gametes, the young embryo.

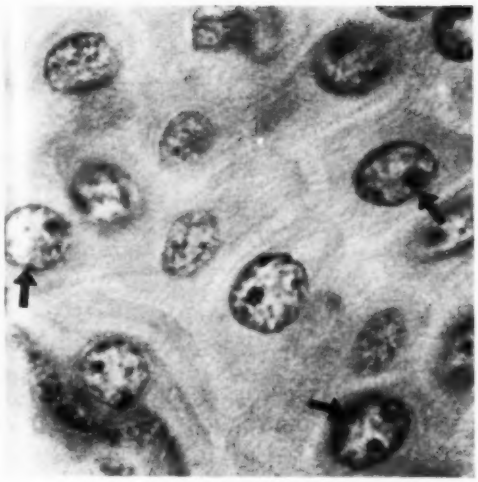

FIGURE 1. Skin biopsy from normal woman. The arrows point to some of the sex chromatin masses in the section.

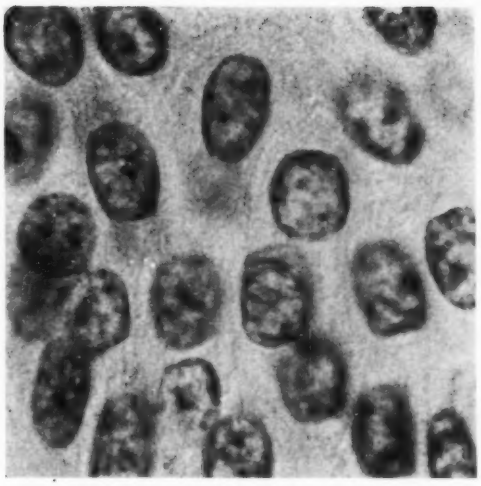

FIGURE 2. Skin biopsy from normal man. Note absence of sex chromatin masses.

remainder of the chromatin an affinity for basic dyes and, consequently, reacts positively to tests for desoxyribonucleic acid, staining readily with the Feulgen technic and with methyl green. In particularly favorable circumstances, as in the study of whole mounts of thin membranes, the sex chromatin can be identified in virtually every nucleus. In sections of tissues 5 μ in thickness, sex chromatin can be identified in 60 to 80 per cent of the nuclei, depending on the technical quality of the preparations and such factors as the size of the nuclei and the coarseness of the general chromatin particles. Human skin,[4,5] scrapings from the buccal mucosa,[6,7] exfoliated vaginal cells,[8,9] and monocytes and lymphocytes[10] all provide readily available sources of material for the identification of this sex-specific characteristic. Neutrophils[11] have a different kind of sexual dimorphism. In a small proportion of neutrophils of females (1 to 10 per cent), there is an accessory nuclear lobule; such a lobule is encountered with the greatest rarity, if at all, in neutrophils of males. Recently it has been possible to obtain reliable cytogenetic information from bone marrow specimens which have been cultured briefly after removal from the body.[12]

TABLE 1

SEX CHROMATIN TEST IN NORMAL MALES AND FEMALES

	NUMBER OF CASES	PERCENTAGE OF NUCLEI WITH SEX CHROMATIN MASSES
Skin biopsies (males)	105	4.5 (1 to 12)
Oral smears (males)	198	0.7 (0 to 4)
Skin biopsies (females)	86	69.2 (51 to 82)
Oral smears (females)	127	54.1 (20 to 79)

Since the sex chromatin is a Feulgen-positive chromocenter, it presumably represents positively heterochromatic regions of the two X chromosomes of female cells; that is, regions that are dense and prominent when the euchromatic regions are indistinct. The fine details of the sex chromatin, especially its bipartite structure and its connection with a delicate thread that may also be double, as well as the multiple masses of sex chromatin that are present in polyploid nuclei, suggest that it is formed from the heterochromatic regions of a pair of homologous chromosomes.[3,13] An alternative interpretation, suggested by Segal and Nelson,[14] is that the heterochromatic mass may represent intermitotic allocyclic regions of an autosomal pair containing male-determining factors. The first interpretation implies somatic pairing of the

TABLE 2

SEX CHROMATIN TEST IN CASES OF SEXUAL DYSGENESIS
(No Distinction Between Skin Biopsies and Oral Smears)

SEX OF REARING	NUMBER OF CASES	NUCLEI WITH SEX CHROMATIN (PER CENT)	RANGE (PER CENT)	SEX DIAGNOSIS	
				Male	*Female*
KLINEFELTER'S SYNDROME					
Male	72	49.6	21-82		72
Male	16	1.3	0-3	16	
GONADAL AGENESIS					
Female	120	2.8	0-14	120	
Female	24	50.9	25-83		24
MALE PSEUDOHERMAPHRODITISM (Testicular feminization syndrome)					
Female	26	4.6	0-10	26	
CONGENITAL ADRENAL HYPERPLASIA					
Female pseudohermaphrodites					
Female	70	56.4	26-79		70
Male	7	56.8	32-74		7
Macrogenitosomia precox					
Male	6	2.3	0-4	6	

X chromosome. This assumption of somatic pairing of the X chromosome has generally unsatisfactory aspects, although it should be said that Ohno, Kaplan and Kinosita[15] reported evidence in the mouse for somatic association of the X chromosomes in epithelial cells of ovarian follicles and the mammary gland. In other types of cells that were examined, this association was not found. In their study on nuclei of regenerating liver in the rat, Ohno and his associates observed a distinctive chromocenter in interphase nuclei of females, but not of males. During prophase, when the chromosomes can be identified, neither the X nor the Y chromosome of the male seemed to differ in its heterochromatic properties from the autosomes. But in prophase nuclei of females, the surprising observation was made that one X chromosome was positively heterochromatic, while the other X chromosome was isochromatic with respect to the autosomes. Ohno and his collaborators suggest that the positively heterochromatic X chromosome may be of paternal origin. If this is true, the sex chromatin mass seen in females is the manifestation of the X chromosome contributed by the paternal parent. Males would, of course, lack this chromosome.

Further complication in interpreting the meaning of the sex chromatin mass seen in females was introduced by the studies of Kosin and Ishizaki,[16] who claimed that the presence of sex chromatin in somatic-cell nuclei is a female characteristic in the chicken. Since in fowls the female is the heterogametic sex, the chromatin cannot in this instance be a derivative of two homologous sex chromosomes. In fowls the sex chromatin complement in males is designated as ZZ; in females, ZO (Z being the only sex chromosome present in females). It seems, on this basis, that the sex chromatin in female fowl must be a derivative of the single Z chromosome, unless it bears no direct relationship to the sex chromosomes. It should be noted that several earlier studies on avian tissue had failed to note sexual dimorphism in the nuclei of somatic cells, and that the work of Kosin and Ishizaki must have confirmation before it is regarded very seriously.

Chromosomes in Man

For many years, the diploid number of chromosomes in normal men and women was believed to be 48. This accepted count has been revised following the observations of Tjio and Levan,[17] of Ford and Hamerton,[18] and of Ford and Jacobs,[12] all using improved methods. There no longer appears to be any doubt that the correct number is 46: 22 pairs of autosomes and one sex chromosome pair, XX or XY. Discovery of the sex chromatin mass and subsequent recognition of its regular occurrence in normal females of many mammalian species have provided a new approach to the study of human intersexual conditions, especially when studies have been combined with the new methods for chromosomal detection. Furthermore, there is no doubt that the recent reports of chromosome abnormalities in man will increase our understanding of human genetic mechanisms. Certain anomalies of sex differentiation which have been studied by the method of nuclear sexing and clarified further by chromosomal procedures have provided an extraordinarily interesting addition to the understanding of the development of the human reproductive system.

Klinefelter's syndrome—This interesting disturbance of gonadal function has taken on added interest as a result of the application of the technics for diagnosis of "genetic" sex. In this syndrome, seen about once in every 500 males, the testes are always much smaller than normal, and the seminiferous tubules usually are hyalinized completely or have Sertoli cells only. However, germinal cells can be identified in a few tubules in some specimens, even to the stage of mature sperms in occasional tubules. Azoospermia has been a constant finding. Leydig cells are variable in number and functional appearance, but tend to occur in clumps of some size. Eunuchoid traits of varying extent and gynecomastia are seen in approximately 50 per cent of the cases. Urinary gonadotropins are elevated, and estimations of urinary 17-ketosteroids and estrogens show values ranging from normal to moderately low.

The nuclei are chromatin-positive in most instances (our data are given in table 2), and there is a fair degree of correlation between testicular pathology and nuclear structure, the testes tending to be less abnormal when the nuclei are chromatin-negative.[19] Some studies have suggested that the chromatin-positive cases might be due to a chromosomal aberration, and it was suggested that the defect might, in some instances, be transmitted through the paternal line as a sex-controlled dominant character which is not sex-linked.[20] However, the majority of observations, including those with sibship data, indicated that all such cases could not be familial and that the majority appeared to be of sporadic occurrence. The possibility of heteroploidy has been considered, as well as translocation of genes by inversion crossover.

With the development of dependable methods for the study of chromosomes, it was obvious that cases of the Klinefelter syndrome should be examined. When such studies were made by Jacobs and Strong,[21] and subsequently by others, it became evident that in chromatin-positive cases of Klinefelter's syndrome 47 chromosomes are present. This was determined by finding one Y and two X chromosomes. On the other hand, chromatin-negative cases showed only 46 chromosomes. Parents of patients with 47 chromosomes were examined and were found to have the normal number of 46. The occurrence of the extra chromosome, therefore, may be due to nondisjunction of the sex chromosomes at either mitosis or meiosis during gametogenesis in one or the other parent. Alternatively, it may be due to nondisjunction occurring during the subject's very early embryologic development, in which case there is a possibility that the individual may be a mosaic (inconstant number of chromosomes). Ford and associates[22] have described an XX/XXY "mosaicism" in a patient with Klinefelter's syndrome, counts of chromosomes in a number of cells revealing 46 in some and 47 in others. They assumed that the 46 chromosome cells contain two X chromosomes and no Y chromosome, i.e., the normal female complement. The supposition is that this mosaic individual developed from an XXY zygote, this zygote arising through

fertilization of a nondisjunctional XX egg by a normal Y sperm, or of a normal X egg by a nondisjunctional XY sperm.

The presence of an XXY complex in cases of chromatin-positive Klinefelter's syndrome has been confirmed by many laboratories. Colorblindness studies[23,24] not only confirm the presence of two X chromosomes, but suggest that the condition is caused by abnormalities of the first meiotic division of oogenesis or spermatogenesis, or of the second meiotic division of oogenesis.[25,26]

The *Drosophila* type of sex determination has been taken so frequently as a model that it is important to point out that in Klinefelter's syndrome, the XXY individual presents a male phenotype, whereas in *Drosophila*, the XXY fly is a fertile female.[27] If cases of chromatin-positive Klinefelter's syndrome should prove to be the first instances of a general rule for man, the indication would be that the Y chromosome in man is strongly "male-determining" in contrast to the Y chromosome of *D. melanogaster*, which is essentially inert in relation to development of the sex phenotype, although necessary for male fertility. The convincing demonstration by Welshons and Russell[28] and Russell, Russell and Gower[29] that mice with an XO sex chromosome constitution are fertile females, and thus that the mouse Y chromosome is male-determining, lends strong support to this argument as applied to mammalian species.

Mongolism—This condition of congenital mental deficiency is accompanied by various other defects. The finding that some persons with Klinefelter's syndrome show evidence of mental deficiency and have an XXY sex chromosome complement stimulated extension of such investigation to cases of mongolism.[13,30,31]

Examination of blood and buccal smears in mongoloids showed the males to be chromatin-negative and the females chromatin-positive. When chromosomal methods were applied in both sexes, the diploid number was found to be 47, instead of 46. It appears, therefore, that the condition of mongolism is associated with the presence of an extra chromosome. Jacobs et al.[32] think this additional chromosome is an acrocentric chromosome in the smallest size range, where the Y chromosome is also to be found. They were unable to detect a difference in the remaining 46 chromosomes from those of the normal diploid set. It is not likely that the extra chromosome is a Y chromosome. If it were, the female mongoloid would have the genetic constitution XXY, which is the chromosomal complement associated with the chromatin-positive cases of Klinefelter's syndrome. The presently accepted explanation is that mongolism may have its origin in the events of oogenesis, whereby the trisomic state of one of the smallest acrocentric autosomes probably arises as a result of failure of a pair of homologous chromosomes to separate. This may occur during either meiotic or mitotic division of the germ cell. If both chromosomes pass to the same nucleus and fertilization by a normal male gamete occurs, the result would be an individual with the trisomic condition, i.e., $2n+1$, the value of n for man being 23.

A somatic-cell chromosome number of 48 has been found in a unique individual with both mongolism and Klinefelter's syndrome.[33,34] Each cell of this individual appeared to contain a normal set of 23 pairs, as in a normal female, plus a Y chromosome and an extra acrocentric chromosome. This appears to be the first time that a human being with two supernumerary chromosomes has been described, i.e., an XXY sex chromosome complex associated with Klinefelter's syndrome and the additional small autosome characteristic of mongolism.

Gonadal dysgenesis (Turner's syndrome)—The only important abnormality of the reproductive system in this condition is virtual absence of ovaries in a female, the "ovaries" being represented, usually, by slender streaks of connective tissue. While the syndrome may go undetected until puberty, when development of secondary sex characteristics and menarche fail to occur, various visible congenital defects frequently call attention to the presence of the syndrome during the prepuberal period or even in the newborn child. There may be lymphedema of the lower extremities during the neonatal period and nuchal folds or short stature may be sugges-

tive signs in children. Various skeletal anomalies and coarctation of the aorta occur occasionally. Urinary gonadotropins are elevated after the age of 10 to 12 years, as in the manner of the castrate.

Sex chromatin studies have been made in many of these cases, and the majority of individuals proved to be chromatin-negative, in spite of their essentially female anatomy. Table 2 presents data on our material.

When the new chromosomal methods were applied to sex chromatin-positive cases, the chromosome number was noted as 46, the normal number, and the sex chromosome constitution as XX. The cases of the syndrome with sex chromatin-negative patterns proved to be of more interest, since the somatic cells contained only 45 chromosomes, with a sex chromosome complement determined as XO.[35-37] These individuals are female anatomically, have somatic cells judged to be "male" by nuclear sexing, and possess a sex chromosome complement that is neither normally male nor normally female.

Cases of this type can be understood on the basis of failure of gonadal development at a very early stage of embryonal life. In the absence of gonads, the female phenotype develops regardless of the chromosomal sex of the individual. In this regard it is not the presence or absence of ovaries that is important. Rather it is the absence of *functional* testes.[37] That the mere presence of testes is insufficient to direct development along masculine lines is emphasized by the situation in the syndrome of testicular feminization which will be discussed later in this paper.

The bulk of evidence indicates that testes develop only in individuals who have a Y chromosome and that the presence of a Y chromosome can override the influences of two X chromosomes, as in the case of Klinefelter's syndrome. On the other hand, a single X chromosome, or even two X chromosomes, may not be sufficient to promote development of ovaries, as is shown by the lack of ovaries in both chromatin-negative and chromatin-positive cases of Turner's syndrome. In this regard, the patient reported by Hutchings[38] is of interest. This 13 year old girl was shown to have a negative sex chromatin pattern together with apparently normal ovaries and normal, although immature, female reproductive structures. Chromosomal studies on this case should prove illuminating.

An explanation of the origin of the sex chromosome anomaly seen in cases of Turner's syndrome with an XO sex chromosome complement would seem available in the process of nondisjunction of chromosomes. This abnormality of oogenesis is best understood in *D. melanogaster*.[39] By nondisjunction of the sex chromosomes is meant the fact that both X chromosomes migrate to one pole of the spindle during one of the two meiotic anaphases, leaving the other pole without any X chromosome. As a consequence, the mature ovum is provided with either the haploid number of autosomes plus two X chromosomes or the haploid number of autosomes without X chromosomes. Fertilization of an ovum of the latter type by a Y-bearing sperm results in a nonviable zygote; fertilization by an X-bearing sperm yields an XO zygote which develops into a sterile male. In humans, an XO zygote apparently develops into a sterile "agonadal" individual whose phenotype is female. The other stigmas seen with varying degrees of frequency in Turner's syndrome undoubtedly are due to genetic disturbances that are less well understood at the present time.

Fertilization of the other type of abnormal ovum (XX) by an X-bearing sperm gives, in *Drosophila*, an XXX zygote which usually dies. However, the occasional zygote that does survive shows accentuated female secondary sexual characteristics and is designated as a "superfemale." Fertilization of an XX ovum by a Y-bearing sperm yields an XXY zygote which becomes a fertile female. In man, however, the XXY individual develops as a chromatin-positive case of Klinefelter's syndrome, as previously discussed. A case in which the sex chromosome complement has been considered to be XXX has now been reported (discussed later in this paper), bolstering the evidence in favor of the occurrence of nondisjunction in man.

Although this discussion of nondisjunction has given consideration to oogenesis only,

color-vision studies in cases of families of individuals with gonadal dysgenesis suggest that it may also occur in spermatogenesis. If an O ovum is fertilized by an X sperm and the resultant individual has a major red-green color-vision defect, the father should show the same defect. However, in some families where patients with gonadal dysgenesis (chromatin-negative) showed a major red-green color-vision defect, this was not the case; i.e., the fathers did not have the defect. It would necessarily follow that in these individuals the X chromosome with the anomalous color-vision gene was not of paternal origin, but was contributed by a heterozygous mother. Cases with XO sex chromosome complements and showing major color-vision defects in which the fathers lack this defect must arise, therefore, from the fertilization of normal X-bearing ova by sperm carrying neither X nor Y. Such sperm would arise as a result of nondisjunction during spermatogenesis. Evidence that this is by no means unlikely is provided by the observation that X and Y chromosomes are sometimes unpaired at metaphase in primary spermatocytes.[24-26] Both chromosomes would then be expected to migrate to the same pole in approximately 50 per cent of the ensuing anaphases.

The human "superfemale"—In the discussion of nondisjunction and the discovery of XO and XXY individuals, it was indicated that one would expect the existence of a third type of sex chromosome anomaly, namely, the superfemale, characterized by a chromosomal number of 47 and a chromosomal sex of XXX. Such a case has, indeed, been reported by Jacobs et al.[40] The individual involved is a female of average height, but exhibiting underdeveloped breasts, infantile external genitalia, and a small vagina. A detailed analysis of cells from cultured bone marrow and skin revealed that the great majority contained 47 chromosomes. All cells were found to have an additional chromosome in the same medium-sized range as the X chromosome. It is presumed, therefore, that this patient has an XXX sex chromosome constitution. Support for this presumption is furnished by the observations on sex chromatin in buccal smears and by the fact that her abnormalities seem to be confined to the genital tract. As has already been noted, an additional autosome is known to occur in cases of mongolism. This condition presents numerous anomalies which, however, are unrelated to the reproductive system. On this basis, it is unlikely that the extra chromosome observed in the superfemale is an autosome.

It is now apparent that a condition may exist in man in which the chromosomes number 47, made up of 44 autosomes and three X chromosomes, a circumstance analogous to the superfemale found in *D. melanogaster*. In the latter organism, primary nondisjunction of the X chromosome occurs with a frequency of about 1 in 2000, and eggs containing an XX pair when fertilized by X-bearing sperm give rise to superfemales. In *Drosophila* such superfemales are usually nonviable, but the single case reported for man suggests that in the human being the condition may affect the genital tract only. Of course, it is highly desirable that additional evidence on this as well as all of the recent observations on human chromosomal aberrations should be secured. This area of investigation is very new and undoubtedly some of the claims made will not stand up under further examination.

Testicular feminization—In this syndrome, the external genitalia are female, pubic and axillary hair may be absent or scanty, and the habitus after puberty is typically female. Primary amenorrhea is a constant finding. When search is made for gonads, they are found either within the abdomen, in the inguinal canals, or in the labia majora. Their histologic appearance is typical for undescended testes seen in otherwise normal males. An epididymis and a vas deferens are commonly present on both sides. There may be a rudimentary uterus and fallopian tubes,[41] and the vagina may be incompletely developed.

It is evident that these individuals are "sex-reversed" males, since they have been found to have a normal diploid number of chromosomes and an XY sex chromosome complement in each case that has been studied. The latter is consistent with the observation that skin biopsies and buccal smears show all of

these individuals to be sex chromatin-negative (table 2) and, in addition, excludes an aberration of chromosome number as the cause of the disorder. The condition is known to be familial and may be associated with either a sex-linked recessive gene or a sex-limited autosomal dominant gene.[42] It is difficult to distinguish between these alternatives, since affected subjects are sterile, but some information can be secured by the study of pedigrees having sex-linked recessive characters.

Various genetic studies have demonstrated that an autosomal factor segregates independently of the sex chromosomes, and two sex-linked characters may be separated by crossing over. If the latter characters are not closely linked, crossing over can give the appearance of random segregation. Thus, colorblindness studies, even in a large number of families, may provide no more than limited information concerning the genetics of testicular feminization, although both cytogenetic evidence and the incidence of colorblindness in the condition indicate that subjects with this syndrome have a single X chromosome. Current data suggest that the genetic factors responsible for testicular feminization and colorblindness are not closely linked on the X chromosome, but clearly a study of many pedigrees must be carried out before it will be possible to clarify the hereditary mechanics of the syndrome.[10, 43]

Congenital adrenal hyperplasia—Although this syndrome appears to involve no aberration of sex chromosomal patterns in either sex it may, in its severest expression, lead to the rearing of genetic females as males. It occurs, or at least is recognized, much more frequently in females than in males (see table 2). The reason for this is not surprising since the defect leads to accentuation of masculine development. In females only is such accentuation usually recognized during the neonatal period unless the affected male shows evidence of electrolyte disturbances.

From the standpoint of this discussion the syndrome of congenital adrenal hyperplasia may be regarded as the most common form of female pseudohermaphroditism. There is no abnormality of the gonads, or of the uterus, but in affected females the other secondary sexual organs show varying degrees of masculinization.[14, 19, 41] Usually these abnormalities are confined to clitoral hypertrophy, partial fusion of the labioscrotal folds, and more or less incomplete development of the vagina. Persistence of the defect through the years of childhood and adolescence leads to precocious growth, continued masculinization, and absence of feminine puberty. Suspicion of this defect, which is due to an abnormality of steroid metabolism in the adrenal cortex resulting in excessive production of androgen, is confirmed by the finding of elevated 17-ketosteroids and a normal sex chromatin picture. It is important to establish diagnosis of this defect as early as possible, because correction of its consequences can be effected by the administration of cortisone and, where necessary, by appropriate plastic surgery.

Conclusions

Once every decade or so, several lines of research come into a common focus and stimulate a new train of scientific activity and thought. This situation has occurred very recently as studies on experimental embryology, discovery of the sex chromatin, and development of dependable methods for the study of chromosomes merged and excited the interest of many investigators. The result has been an explosive burst of activity in applying the new methods to a variety of unexplained developmental and genetic aberrations in man. The next few years are certain to provide information of primary importance in the field of human cytogenetics and its application to clinical medicine. However, exciting as developments have been during the past few years and as those to come are likely to be, it is important to recognize that a measure of caution should be exercised in accepting them until adequate confirmation has been given. Although the material included in this discussion has been considered with care, it is not unlikely that a similar review written a year hence will have the benefit of observations which will offer new interpretations and reduce the significance of some of the findings recorded here.

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Anterior Pituitary Hormones

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The adenohypophyseal hormones influence general body growth and carbohydrate metabolism and exercise direct control on the functions of the adrenal cortex, the thyroid and the gonads. The six known hormones of the anterior pituitary are classified as metabolic and gonadotropic.

In describing the biologic properties and physicochemical characteristics of the various anterior pituitary hormones, the author discusses such topics as the hormonal mechanism governing mammary growth and lactation, differentiation of ovine prolactin and bovine prolactin, and the physicochemical differences among the growth hormones, luteinizing hormones and adrenocorticotropins isolated from the pituitary glands of various species.

CHOH HAO LI

Of all the endocrine glands, the anterior lobe of the hypophysis occupies the prime place. In addition to its influence on general body growth and carbohydrate metabolism, the adenohypophysis exercises direct control on the functions of the adrenal cortex, the thyroid and the gonads. Hence, the hormones secreted by the anterior pituitary (except the growth hormone) are called "tropic" hormones; i.e., their function is the stimulation of a specific target organ, an endocrine gland, whose activity is thereby either enhanced or awakened.

There are six known adenohypophyseal hormones whose existence has been firmly established. These six hormones may be classified into two groups, *metabolic* and *gonadotropic*. The metabolic hormones are the thyrotropic hormone (thyroid-stimulating hormone, TSH), adrenocorticotropic hormone (ACTH), and growth hormone (somatotropin, STH). The gonadotropic hormones are follicle-stimulating hormone (FSH), interstitial cell-stimulating hormone (ICSH, luteinizing hormone, LH), and lactogenic hormone (prolactin, luteotropic hormone, LTH, mammotropic hormone, MH). Figure 1 presents a diagrammatic summary of the biologic properties of the pituitary hormones.

Gonadotropic Hormones

In the female, FSH stimulates the development of immature ovarian follicles, bringing them to maturity. ICSH in turn stimulates

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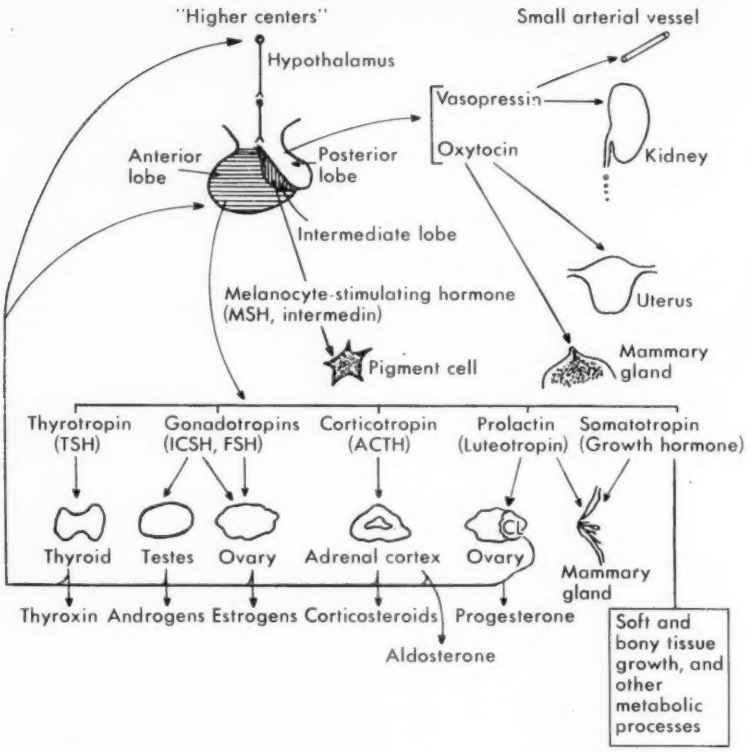


FIGURE 1. Diagrammatic summary of the biologic properties of pituitary hormones. (CL, corpus luteum.)

From Bell.[28]

the mature follicles to form estrogens and gives the follicle impetus for further development as a corpus luteum. The growing corpus luteum is then brought to maturity by LTH. The secretion of progesterone from the functional corpora lutea is under the control of LTH. Figure 2 outlines the action of the pituitary gonadotropic hormones in the female.

Little is known about the physiologic function of FSH except that it promotes follicular growth in both normal and hypophysectomized immature animals. The known biologic properties of ICSH may be summarized as follows: (1) accomplishing repair of ovarian interstitial tissue; (2) stimulating the seminiferous tubules and the interstitial cells in the male, eliciting the production of androgen which in turn causes enlargement of the accessory organs; (3) causing formation of corpora lutea and production of estrogen when injected subcutaneously in conjunction with FSH; (4) eliciting ovulation; (5) prolonging the diestrous interval and gestation; (6) stimulating spermatogenesis.

The isolation of ICSH in highly purified form from sheep, pig and human pituitary glands has been reported.[1,2] Physicochemical and immunologic studies indicate that the hormones derived from human and sheep glands are not identical (see table 1). Purified preparations of FSH have also been obtained from sheep, pig and human pituitaries. Of all the pituitary hormones, FSH appears to be the only one which is soluble in a half-saturated $(NH_4)_2SO_4$ solution. Both FSH and ICSH preparations appear to contain carbohydrates[3] in addition to their constituent amino acids. Table 2 gives recent data on the carbohydrate content in purified preparations of human and ovine gonadotropins.

The first indication that a hormone from the anterior pituitary might bring about lactation in mammals came from early experiments (1928) which showed that lactation could be

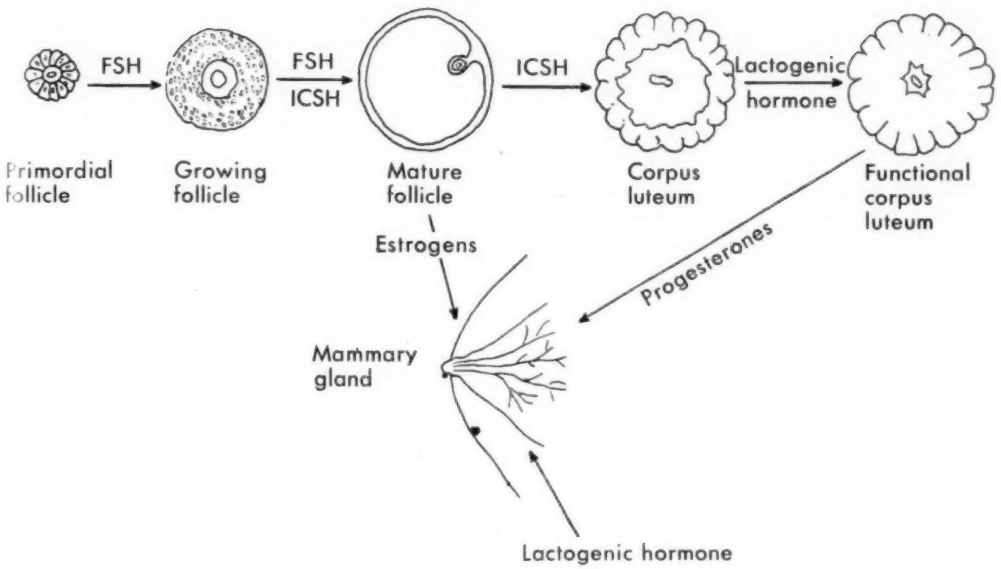


FIGURE 2. Action of pituitary gonadotropic hormones in the female.

From Li.[3]

elicited in the pseudopregnant rabbit, before and after spaying, by the injection of an anterior pituitary extract. These observations have been confirmed and extended by a number of investigators. In 1931, it was demonstrated that macroscopically observable growth of the crop glands of the pigeon occurs after the administration of pituitary extracts. Subsequent work has indicated that this effect in the bird is probably due to the same factor that induces lactation in mammals.

The most convenient and satisfactory methods for assaying the activity of lactogenic hormone are those based on the response of the crop glands of the pigeon. The luteotropic or corpus luteum-stimulating potency of prolactin may be estimated on the basis of the formation of grossly observable deciduomas induced in the threaded uterus of the hypophysectomized rat by the progesterone secreted by the stimulated luteal tissue. Highly purified preparations of lactogenic hormone have been obtained from both beef and sheep pituitary glands.

Earlier observations that *ovine* prolactin can be differentiated from the *bovine* hormone by differences in solubility behavior and in tyrosine content have now been confirmed. Table 3 presents a summary of the known physical and chemical properties of bovine and ovine prolactin;[4] both preparations have a molecular weight of approximately 25,000 and an isoelectric point at pH 5.73. The hormone protein consists of a single peptide chain with 211 amino-acid residues, and with the sequence Thr.Pro.Val.Thr.Pro at the N-terminus and an interchain disulfide loop at the C-terminus.

The hormonal mechanism which governs mammary growth and lactation has been completely elucidated in the rat during the past few years. According to these investigations,[5,6] pituitary FSH and ICSH synergize to stimulate the ovary to secrete estrogenic hormones. The estrogens act together with the growth hormone and adrenal steroids secreted under the influence of ACTH to induce mammary ductal growth. The lactogenic hormone activates the corpus luteum to secrete progesterone, and the prolactational combina-

TABLE 1

COMPARISON OF HUMAN AND SHEEP ICSH

PROPERTIES	ICSH	
	Human	*Sheep*
Leak point*	pH 5.6	pH 6.2
Sedimentation coefficient ($s_{20,\ w}$)	2.14 S	2.47 S
Isoelectric point	<<pH 7.3	pH 7.3
Dose-response equation†	P=24.8 log D+0.6‡	P=7.2 log D+12.1

*Amberlite IRC-50 resin equilibrated with 0.2M potassium phosphate buffer.

†Male rats were hypophysectomized at 21 days of age; subcutaneous injections were begun two days after the operation and were administered daily for four days. Autopsy was done 24 hours after the final injection.

‡P=ventral prostate weight in milligrams; D=dosage in micrograms.

tion of growth and lactogenic hormones plus estrogen plus progesterone plus adrenal hormone induces full lobuloalveolar development (see figure 3). For lactogenesis, lactogenic hormone and adrenal hormones play a dominative role; growth and thyrotropic hormones are important for the normalcy of lactating conditions, but they are not necessary for lactogenesis.

Purified preparations of human FSH have been shown to be highly active in female subjects.[7,8] Although human ICSH has not been tested in man, it is expected to be potent in inducing ovulation and spermatogenesis. The activity of ovine prolactin in man has been the subject of occasional studies, but clear-cut clinical usefulness of the hormone has yet to be shown. It is likely that prolactin from human pituitaries will be found to differ chemically from the hormone prepared from the glands of domestic animals.

Metabolic Hormones

The anterior pituitary hormones which control and regulate body metabolism are the thyrotropic, adrenocorticotropic and growth hormones. Thyrotropic hormone stimulates the thyroid gland to secrete its hormone, thyroxin, and ACTH stimulates the adrenal cortex to produce cortisol, aldosterone and other adrenocortical hormones. Growth hormone influences the general process of body growth. The metabolic functioning of the body depends on the balance of the interaction among these hormones (see figure 4).

Purified TSH preparations have been obtained from beef glands[9,10] in highly purified form; they have a molecular weight in the neighborhood of 28,000 and possess an activity of 20 to 50 units per milligram. Clinical investigations of these preparations have shown that they are active in man. No report on the purification of TSH from human pituitaries has appeared.

From clinical observations of disturbances in the growth process, which are possibly the most obvious to perceive of all endocrine results, it was evident very early that the pitui-

TABLE 2

CARBOHYDRATE CONTENT OF OVINE AND HUMAN PITUITARY FSH AND ICSH PREPARATIONS*

PITUITARY	PREPARATIONS	CARBOHYDRATE CONTENT,† MILLIGRAMS PER 100 MG. PROTEIN			
		Hexose	*Fucose*	*Hexosamine*	*Sialic acid*
Sheep	FSH	2.30	0.43	3.55	2.44
	ICSH	3.23	0.74	6.26	0.80
Human	FSH	2.10	0.45	2.80	1.89
	ICSH	1.12	0.35	1.95	0.96

*From Gröschel and Li.[3]

†Average value taken from two to six determinations.

TABLE 3

SOME PHYSICAL AND CHEMICAL PROPERTIES OF PROLACTIN FROM SHEEP AND BEEF PITUITARY GLANDS

PROPERTIES	SHEEP	BEEF
Molecular weight	24,200	26,000
Isoelectric point, pH	5.73	5.73
Partition coefficient*	1.58	2.07
Tyrosine, per cent (by weight)	5.26	6.62
Tryptophan, per cent (by weight)	1.69	1.75
Cystine, residue/mole	3	3
N-Terminal amino acid	Threonine	Threonine
C-Terminal amino acid	Half cystine	Half cystine

*2-Butanol/0.35 per cent aqueous dichloroacetic acid.

tary gland bears a direct relationship to body growth. Early specific experiments confirmed these general clinical observations, offering a convincing argument that the anterior pituitary secretes a hormone which possesses growth-promoting activity. Final proof came with the isolation, in highly purified form[11,12] from beef pituitary glands, of a hormone known as *growth hormone* (from its obvious effects on growth) or *somatotropin* (from *soma*, the Greek word for *body*, since the sphere of the hormone's influence is general body growth).

Although the effects of the bovine growth hormone were readily evident in the rat and mouse, it seemed to be ineffective in humans. Evidence was gathered by a number of investigators which pointed to an important connection between the biologic effectiveness of the hormone and the species from which it was derived.[13,14] For example, it was found that the bovine hormone is inactive not only in humans but also in monkeys, whereas the hormone preparation from monkey glands is effective in that particular species. In the same way, a growth hormone concentrate prepared from fish pituitaries is effective in fish but not in rats. The bovine hormone, however, is effective in both fish and rats, although it has also been reported to have no effect in the guinea pig. All this evidence suggested that the growth hormones isolated from various species may not be chemically identical.

This was borne out in 1956, when highly purified preparations of growth hormone were successfully isolated from both human and monkey pituitaries.[15,16] Chemical studies on these preparations have clearly demonstrated a difference between the primate growth hormones and the bovine hormone; for example, the former hormones have a lower molecular weight and a more acidic isoelectric point. Furthermore, structural investigations show that the molecule of the bovine growth hormone has the form of a branched polypeptide chain, whereas the human and monkey hormones consist of a single polypeptide chain. Growth hormone prepared from either whale or pig pituitaries has also been reported recently and, again, these preparations have been shown to have different physical and chemical characteristics from the growth hormones of other species. Structurally, the whale and pig growth hormones are closer to the human than they are to the bovine hormone. Table 4 summarizes the physicochemical properties of the growth hormones from different species, which have been isolated in a highly purified state.

Monkey and human growth hormones prepared by different methods in various laboratories have been administered to human subjects, including hypophysectomized and dwarf patients. In these clinical trials[16-21] the effectiveness of the primate hormones in human subjects was clearly demonstrated, in contrast to earlier clinical failures with the bovine hormone. It has also been demonstrated that a single human pituitary (the average weight of the gland in adult humans is about 750 mg.) contains approximately 3 to 5 mg. of growth hormone.

Immunologic studies conducted with bovine and human growth hormones have demonstrated that the protein hormones form antibodies specific to the species, as evidenced by results of precipitin ring tests with rabbit antiserum and of anaphylactic shock experiments in guinea pigs. It has also been demonstrated in hypophysectomized rats that the rabbit antiserum possesses specific antihormone ac-

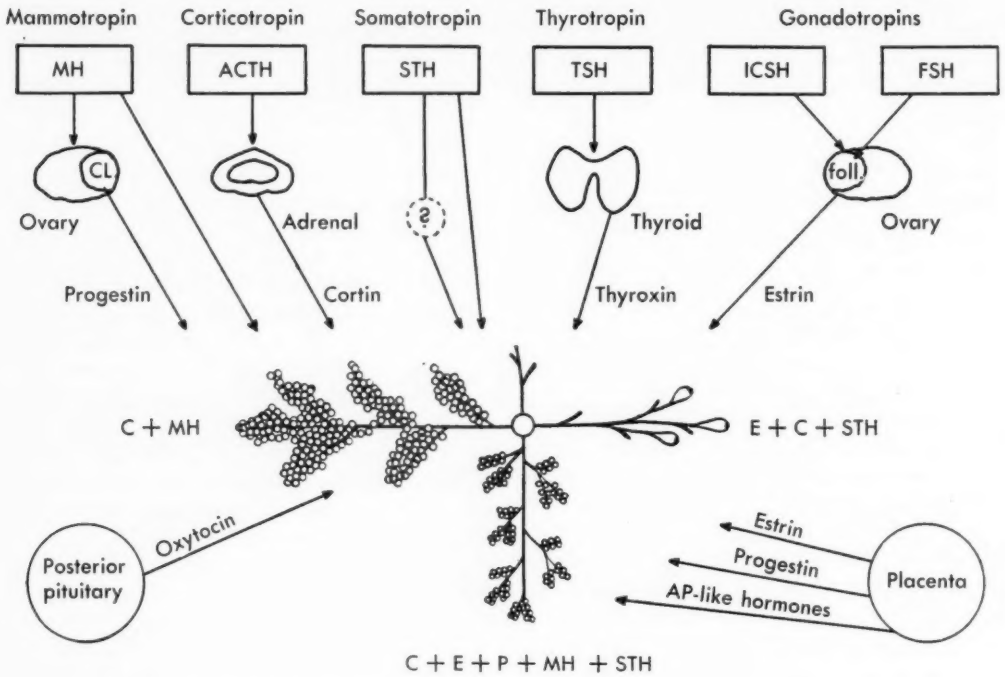


FIGURE 3. Schema showing some of the hormones that influence mammary growth and lactation. In the mammary diagram, the upper portion represents the rudimentary gland, the right portion the prepuberal to puberal gland, the lower portion the gland of pregnancy (prolactational), and the left portion the lactating gland. (C, corticoids or cortin; E, estrogens or estrin; P, progesterones or PROGESTIN®; MH, mammotropin or lactogenic hormone; STH, somatotropin or growth hormone.)

From Lyons, Li and Johnson.[5]

tivity. Moreover, it was shown by the same technics that antibodies to human growth hormone cross-react almost completely with the simian hormone but manifest no reaction with the bovine, ovine, porcine or cetacean hormones. Based on these observations, a quantitative precipitin test, in which purified gammaglobulin is used as the antibody, has been employed to achieve a quantitative estimation of the growth hormone content in single human pituitary glands and in the serum of acromegalic subjects.[22] A preliminary estimate of the growth hormone content in the lyophilized serum of several acromegalic patients, made on the basis of the quantitative immunochemical method, was approximately 0.2 μg. of the hormone per milliliter of serum.

It is of considerable interest that according to all the afore-mentioned data and reports, growth can be elicited in the rat by injections of pituitary somatotropin from practically all the species studied so far, including ox, sheep, whale, pig, monkey and man, with the only exception being the hormone from fish glands. In view of the fact that there are marked differences among these various growth hormones in chemical structure and physicochemical characteristics, it is remarkable that the rat is capable of such a wide response. On the other hand, although it has been demonstrated that man can respond to the growth-promoting activity in primate somatotropins, practically all attempts heretofore to obtain a response in man with the bovine hormone have failed. The question has been raised whether a common biologically active core might possibly exist in the somatotropin molecules derived from various species, and,

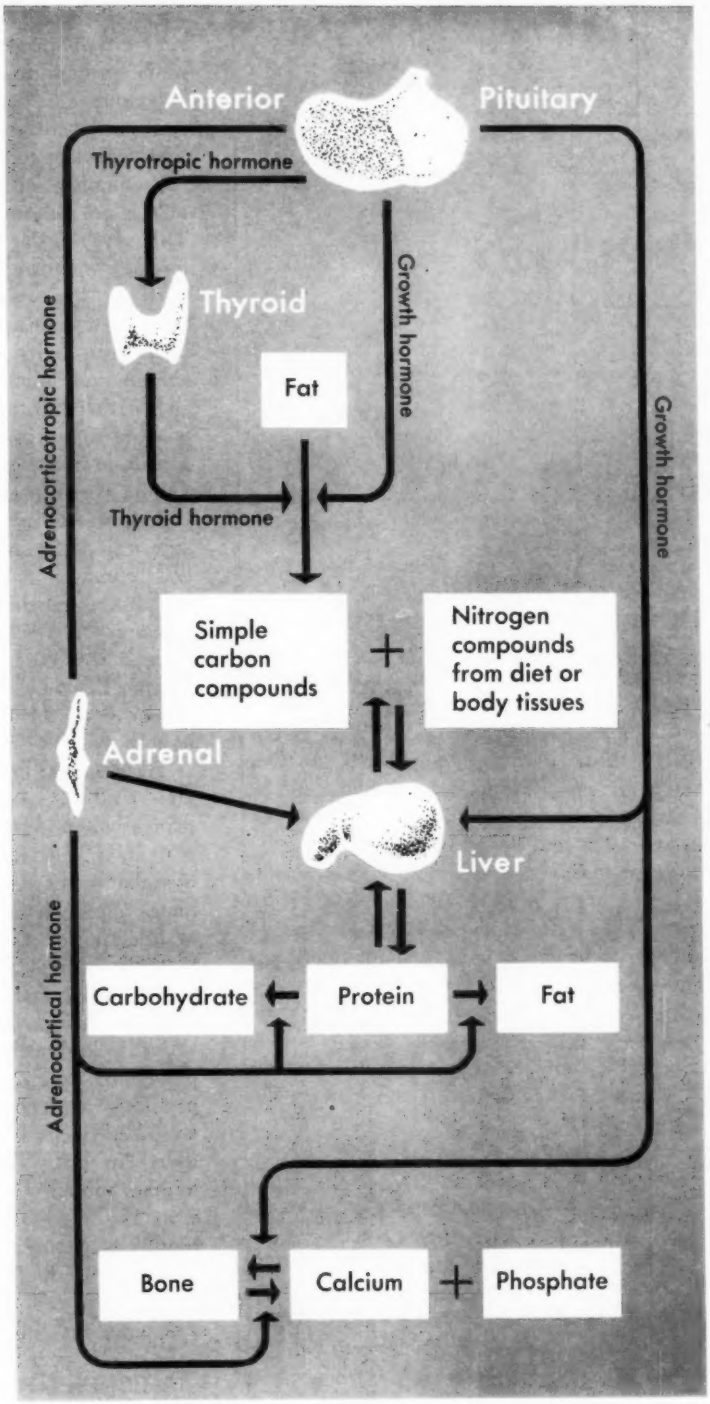


FIGURE 4. Diagrammatic summary of the biologic action of pituitary metabolic hormones.

From Li and Dixon.[29]

TABLE 4

SOME CHARACTERISTICS OF VARIOUS PITUITARY GROWTH HORMONES

PROPERTIES	BEEF	SHEEP	PIG	WHALE	MONKEY	HUMAN
Molecular weight	45,000	48,000	41,000	40,000	25,000	29,000
Isoelectric point, pH	6.8	6.8	6.3	6.2	5.5	4.9
Number of -S-S-bridges	4	5	3	3	4	2
N-Terminal sequences	Phe.Thr.Ala. . . . Ala.Phe.Ala. . . .	Phe. . . . Ala. . . .	Phe. . . .	Phe. . . .	Phe. . . .	Phe.Ser.Thr. . . .
C-Terminal sequence	. . . .Leu.Ala.Phe.Phe	. . . .Ala.Leu.Phe	. . . .(Leu,Ala,Phe).Phe	. . . .Leu.Ala.Phe	. . . .(Ala. Gly).Phe	. . . .Leu.Phe

further, whether the rat may possess the necessary enzyme system to utilize the whole hormone protein from nonprimate sources in a way that man does not.

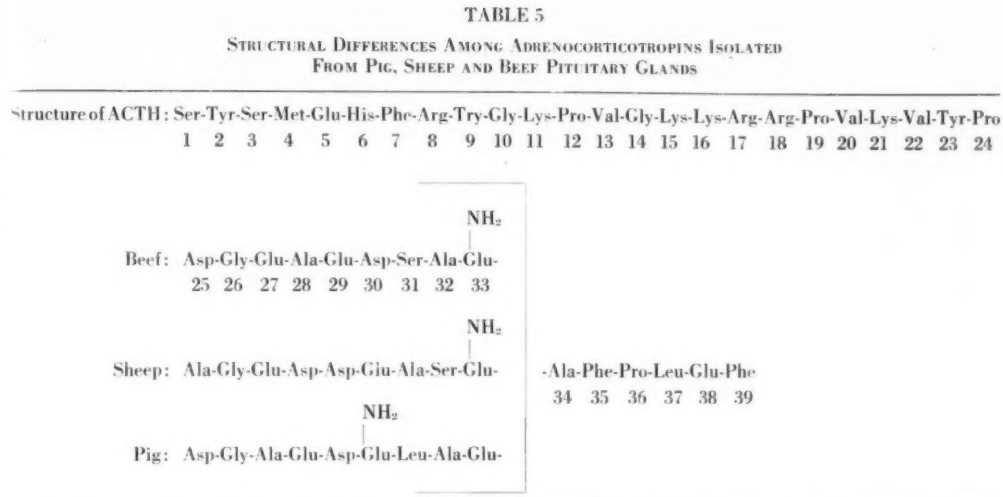
In order to explore this hypothesis, it is first necessary to establish the assumption that the complete integrity of the protein molecule is not necessary for the hormonal action. This was earlier found to be the case for bovine somatotropin[23] when the hormone was partially hydrolyzed with enzymes, chymotrypsin, trypsin and carboxypeptidase. Similar studies with ovine, porcine, cetacean, simian and human somatotropins have also shown that limited digestion of the hormone with chymotrypsin does not cause loss of growth-promoting potency. Indeed, a fraction (alpha core) prepared from a chymotryptic digest of bovine somatotropin[24] has been shown in preliminary studies to produce nitrogen retention in human subjects.[25] It should be pointed out that these observations are not sufficient to verify the assumption that the same active core occurs in various somatotropins, but they do encourage further investigation along the lines of the "common core" hypothesis.

The removal of the anterior pituitary from almost all the species that have been studied brings about a pronounced atrophy of the cortex of the adrenal glands, whereas the medulla is scarcely affected.[26] On the other hand, implantation of anterior pituitary tissue or injection of pituitary extracts into animals that are normal produces as its chief effect a marked hypertrophy of the adrenal cortex. Hence, the name *adrenocorticotropic hormone* (ACTH, adrenocorticotropin) has been employed to designate the active principle in pituitary extracts that accomplishes repair of adrenocortical atrophy following hypophysectomy. In both experimental animals and human subjects, injections of ACTH accelerate the synthesis and secretion of adrenal hormones, including cortisol and aldosterone. Since 1949, this hormone has been employed clinically for remission of rheumatoid arthritis and other metabolic disorders as well as for a diagnostic agent in tests of adrenal function.

ACTH has been isolated in highly purified

TABLE 5

STRUCTURAL DIFFERENCES AMONG ADRENOCORTICOTROPINS ISOLATED FROM PIG, SHEEP AND BEEF PITUITARY GLANDS


Structure of ACTH: Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Try-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
NH2
Beef: Asp-Gly-Glu-Ala-Glu-Asp-Ser-Ala-Glu-
25 26 27 28 29 30 31 32 33
NH2
Sheep: Ala-Gly-Glu-Asp-Asp-Glu-Ala-Ser-Glu-
-Ala-Phe-Pro-Leu-Glu-Phe
34 35 36 37 38 39
NH2
Pig: Asp-Gly-Ala-Glu-Asp-Glu-Leu-Ala-Glu-

form from sheep,[27] pig,[28] beef[29] and human[30] pituitaries. Although all these ACTH preparations have similar biologic properties, they differ slightly in amino-acid composition and in chemical structure. The adrenocorticotropins from sheep, pig and beef pituitary glands are single-chain polypeptides composed of 39 amino acids with serine and phenylalanine as N-terminal and C-terminal residues, respectively.[23,31] The only difference in amino-acid composition between the pig and sheep hormones appears to be one more leucine in the former and one more serine in the latter; this difference is manifested at positions 31 and 32 of the amino-acid sequence, where alanine and serine appear in the ovine hormone and leucine and alanine in the porcine. Although there are no differences in amino-acid composition between the sheep and beef hormones, a difference in amino-acid sequence occurring in a small portion of the polypeptide chain seems to support the conclusion that sheep and beef adrenocorticotropins are distinct chemical entities. Table 5 gives the structural differences existing among these adrenocorticotropins.

In the course of the purification and isolation of ACTH from pituitary glands of various species, it has been observed that every fraction that is adrenocorticotropically active always possesses melanophore-expanding activity.[23] At one time, it was thought by some investigators that ACTH and the melanocyte-stimulating hormone (MSH, intermedin, melanotropin) were identical, and it was even proposed that melanocyte-stimulating activity be taken as a measure of ACTH potency. This confusion became evident once both ACTH and MSH had been isolated in pure form and their chemical structures had been elucidated.

It is now well established that two melanocyte-stimulating peptides are present in pituitary extracts, namely, α-MSH and β-MSH.[32] The isolation and structure of α-MSH from pig pituitaries have been achieved by Lerner and his co-workers;[32,33] it is a 13-amino-acid polypeptide with an N-acetyl-serine and a valine amide as N-terminal and C-terminal residues respectively:

CH_3CO-Ser.Tyr.Ser.Met.Glu.His.Phe.Arg.
1 2 3 4 5 6 7 8
Try.Gly.Lys.Pro.Val.NH_2
9 10 11 12 13

Recent experiments have also shown that α-MSH from beef and that from horse pituitaries have the same composition and structure as the pig hormone.[34]

In the case of β-MSH, the hormone isolated from the beef glands differs from the porcine hormone by the presence of a neutral amino

TABLE 6

THE RELATION OF THE PARTIAL STRUCTURE OF ADRENOCORTICOTROPINS (ACTH) TO THE STRUCTURE OF MELANOTROPINS (MSH)

ACTH: (Pig, sheep, beef)											Ser. 1	Tyr. 2	Ser. 3	Met. 4	Glu. 5	His. 6	Phe. 7	Arg. 8	Try. 9	Gly. 10	Lys. 11	Pro. 12	Val. 13	Gly. 14	Lys. 15	Lys. 16	Arg. 17	Arg. 18	Pro 19
α-MSH: (Pig, beef, horse)					CH_3CO-						Ser. 1	Tyr. 2	Ser. 3	Met. 4	Glu. 5	His. 6	Phe. 7	Arg. 8	Try. 9	Gly. 10	Lys. 11	Pro. 12	Val. 13	NH_2					
β-MSH: (Pig)	Asp. 1	Glu. 2	Gly. 3	Pro. 4							Tyr. 5	Lys. 6		Met. 7	Glu. 8	His. 9	Phe. 10	Arg. 11	Try. 12	Gly. 13	Ser. 14	Pro. 15	Pro. 16	Lys. 17	Asp 18					
β-MSH: (Beef)	Asp. 1	Ser. 2	Gly. 3	Pro. 4							Tyr. 5	Lys. 6		Met. 7	Glu. 8	His. 9	Phe. 10	Arg. 11	Try. 12	Gly. 13	Ser. 14	Pro. 15	Pro. 16	Lys. 17	Asp 18					
β-MSH: (Horse)	Asp. 1	Glu. 2	Gly. 3	Pro. 4							Tyr. 5	Lys. 6		Met. 7	Glu. 8	His. 9	Phe. 10	Arg. 11	Try. 12	Gly. 13	Ser. 14	Pro. 15	Arg. 16	Lys. 17	Asp 18					
β-MSH: (Human)	Ala. 1	Glu. 2	Lys. 3	Asp. 4	Glu. 5	Gly. 6	Pro. 7	8			Tyr. 9	Arg. 10		Met. 11	Glu. 12	His. 13	Phe. 14	Arg. 15	Try. 16	Gly. 17	Ser. 18	Pro. 19	Pro. 20	Lys. 21	Asp 22					

acid, serine, in place of glutamic acid in position 2:[4]

Asp.Ser.Gly.Pro.Tyr.Lys.Met.Glu.His.Phe.
1 2 3 4 5 6 7 8 9 10

Arg.Try.Gly.Ser.Pro.Pro.Lys.Asp
11 12 13 14 15 16 17 18

When α-MSH and β-MSH are compared structurally with the adrenocorticotropins, it becomes evident that a heptapeptide, Met.Glu.His.Phe.Arg.Try.Gly, occurs in both ACTH and MSH preparations. Moreover, the complete amino-acid sequence of α-MSH is identical with the sequence of 13 amino acids from the N-terminus of the adrenocorticotropins, except that in α-MSH the α-amino group of the N-terminal serine is acetylated and the C-terminal carboxyl residue then becomes an amide.

What is most interesting is the presence of the same heptapeptide (Met.Glu.His.Phe.Arg.Try.Gly) in all preparations of ACTH and MSH, including β-MSH from human[35] and horse[36] pituitaries (table 6). Differing amino-acid sequences on both sides of this heptapeptide result in a different degree of MSH activity and account for the adrenocorticotropic function. Indeed, chemical synthesis of peptides related to this "MSH peptide core" showed that the pentapeptide His.Phe.Arg.Try.Gly is active in darkening an isolated frog skin as well as in hypophysectomized frogs.[37,38] It can thus be said that the presence of the heptapeptide in ACTH molecules is probably responsible for the melanocyte-stimulating activity in adrenocorticotropins. These observations have led to some interesting speculations. For instance, the increased pigmentation in patients with Addison's disease is most probably due to the increased concentration of ACTH in the blood, which is known to occur in conditions of adrenal insufficiency.

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Postgraduate Clinical NOTES

153. GENETICS IN DIABETES

It has been known for hundreds of years that diabetes frequently occurs in more than one member of the same family, but it was not until 25 years ago that the genetic component of this disease was firmly established. Since then, researchers studying family histories have attempted to predict the age at onset of diabetes in children of diabetic parents, hoping to be able to say that after a given age the risk for any particular person would be essentially nil.

More recently, however, Arthur Steinberg, and others at Western Reserve University, Cleveland, Ohio, have shown that the parent's age at onset cannot be used to predict either the child's age at onset or the end of the period of risk for the child. The scientists studied 301 pairs of diabetic parents and children and found that although the majority of children had become diabetic at an earlier age than had their parents, the number was no greater than that expected to occur by chance alone, when no biological relationship is assumed to exist between the age of onset in the parent and in the child.

Research highlights in aging, *Public Health Service Publication*, no. 779, 1959, pp. 1-50

Clinical Aspects of Anterior Pituitary Failure

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Anterior pituitary failure may be idiopathic or secondary to lesions that damage the anterior pituitary gland or interfere with its blood supply.

The clinical syndrome of anterior pituitary failure in adults is primarily the result of decreased production of one or more of several tropic hormones.

With proper diagnosis and treatment, patients with anterior pituitary failure can lead practically normal lives.

ALTHOUGH the anterior pituitary gland, or adenohypophysis, elaborates a number of tropic hormones, as listed by Li[1] in the paper elsewhere in this issue, the clinical syndrome of anterior pituitary failure† in adults is primarily the result of decreased production of one or more of several tropic hormones, namely, gonadotropin, thyrotropin and adrenocorticotropin. Deficiency of these substances, in turn, leads to failure of the gonads, thyroid gland and adrenal cortices. It is the failure of these target glands that gives rise to most of the clinical findings associated with anterior pituitary failure.

With progressive failure of the adenohypophysis, the gonads are usually the first to fail among the target glands, then the thyroid gland, and finally the adrenal cortices. Hence, in some patients there will be failure of the gonads alone, in others failure of the gonads and thyroid gland, and in still others failure of all three glands. The adrenal glands may fail before the thyroid gland, but it is unusual for either of these to fail before the gonads. The clinical picture of anterior pituitary failure is best understood by reviewing first the contributions made to this syndrome by the failure of each of these target glands.

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†Anterior pituitary failure is also called Simmonds' disease, Simmonds' cachexia, hypophyseal failure, hypopituitarism or panhypopituitarism.

The Clinical Picture

Gonads—In men the earliest evidence of gonadal failure is loss of libido and potentia. Concurrently or shortly thereafter, there is prostatic atrophy, which is a sensitive index of testicular failure, and later a decrease in the rate of growth of the beard.

In women, as the ovaries fail, loss of libido

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and cessation of menses without the occurrence of hot flushes are seen. The nipples usually lose their pigmentation, but excessive atrophy of mammary tissue is not common.

In both sexes, with failure of the gonads, there may be thinning or loss of axillary and pubic hair, as well as loss of hair from the trunk, arms and legs. The eyebrows may become thin, especially the lateral portions. Atrophy, paleness and thinning of the skin are common, and the complexion may acquire a pasty, yellowish tinge.

Thyroid gland—Failure of the thyroid gland in anterior pituitary deficiency causes variable changes. Some patients may have the typical appearance (figure 1) and other characteristics of primary myxedema, such as a myxedematous skin, slowed tendon reflexes, and an elevation of the level of plasma cholesterol. However, most patients with anterior pituitary failure do not present these findings (figure 2), even though their failure is severe and of long duration. The reason for these different clinical pictures is not understood. Whether or not the patient with anterior pituitary failure looks myxedematous, as the thyroid fails he usually becomes intolerant to cold, sweating decreases, and a dry skin develops.

Adrenal cortices—Failure of the adrenal cortices may result in weakness, inability to cope with stress, and poor resistance to infection; it probably plays some role in the loss of sexual hair. Patients with adrenal deficiency are notoriously sensitive to the administration of small doses of insulin, and in the past the insulin tolerance test was frequently used in the diagnosis of anterior pituitary failure. This test may cause fatal hypoglycemia, and with better methods for estimating the function of the anterior pituitary there is no real need to employ it at present except in investigative studies. Spontaneous hypoglycemia can also develop in patients with anterior pituitary deficiency, and this too may be fatal. The hypoglycemia is readily controlled by the daily administration of small doses of cortisone.

General factors—In addition to spontaneous hypoglycemia from hypopituitarism, the possibility of multiple endocrine adenomatosis must be considered as a possible cause of hypoglycemia in patients with pituitary tumors. In this syndrome, adenomas of two or more of the endocrine glands are present, including the pituitary gland, islet cells of the pancreas, parathyroid glands, thyroid gland and adrenal cortices.[2] The hypoglycemia results from overproduction of insulin by the islet-cell adenomas of the pancreas and is relieved by surgical removal of these tumors.

Symptoms such as apathy, fatigue and lack of stamina cannot be ascribed to the failure of any particular target gland but probably are caused by the generalized debility that results from failure of the adenohypophysis.

Unfortunately, in the minds of many physicians the term "anterior pituitary failure" creates a mental picture of extreme malnourishment, as exemplified by the patient in figure 3. This patient actually had anorexia nervosa and should be compared with the patient in figure 4, who had severe anterior pituitary failure but was still well nourished. Although loss of weight may be extreme in some cases of anterior pituitary failure, this is unusual, and most patients notice little if any loss of weight, while some may even gain small amounts as their pituitary gland fails.

Patients with intracranial tumors or other lesions in the region of the pituitary gland may complain of loss of vision, headache, and other symptoms referable to the central nervous system.

It should be emphasized that the exact signs and symptoms which will be found in any one patient with anterior pituitary failure de-

FIGURE 1. Patient with primary myxedema, showing typical myxedematous facies.

pend on the severity and duration of the condition, and on the extent to which the gonads, thyroid gland and adrenal cortices have failed.

Laboratory Examination in Anterior Pituitary Failure

Patients with anterior pituitary failure frequently have a low basal metabolic rate, which may be lower than that found in primary myxedema. It may fall to between minus 40 and minus 50 per cent, while in primary myxedema it is unusual for the basal metabolic rate to be much lower than minus 35. Secondary adrenal and gonadal failure and lack of growth hormone are probably responsible for this further decrease in the basal metabolic rate in anterior pituitary failure. As would be expected, the protein-bound iodine of the blood and uptake of radioiodine by the thyroid gland are low. The administration of thyroid-stimulating hormone will cause an increase in the uptake of radioiodine by the thyroid gland; this response helps to distinguish secondary thyroidal failure from primary myxedema. The plasma cholesterol may be normal or elevated.

The urinary excretion of 17-ketosteroids, corticosteroids, pituitary gonadotropins and estrogens is decreased. Likewise, the level of circulating corticoids in the blood is decreased.

FIGURE 2. Patient with severe anterior pituitary failure. Note absence of myxedematous facies.

Sperm production in the male is decreased or absent. Recent studies by Read[3] have shown that the level of growth hormone in the blood of patients with pituitary failure is low or nil.

Although an occasional patient with anterior pituitary failure may have hyponatremia, most of these patients, in contrast to patients with Addison's disease, do not have significant changes in the level of electrolytes in the blood. For the most part, the secretion of aldosterone by the adrenal cortices is considered independent of the function of the anterior pituitary gland; thus patients with anterior pituitary failure can maintain a practically normal electrolytic balance, unless they are subjected to undue stress or illness. Rarely do they need to be given electrolyte-retaining hormones such as desoxycorticosterone acetate or 9-alpha-fluorohydrocortisone. On the other hand, the patients with secondary adrenal failure, as well as patients with primary adrenal failure, are unable to excrete a water load promptly. This is the basis of

FIGURE 3. Patient with anorexia nervosa.

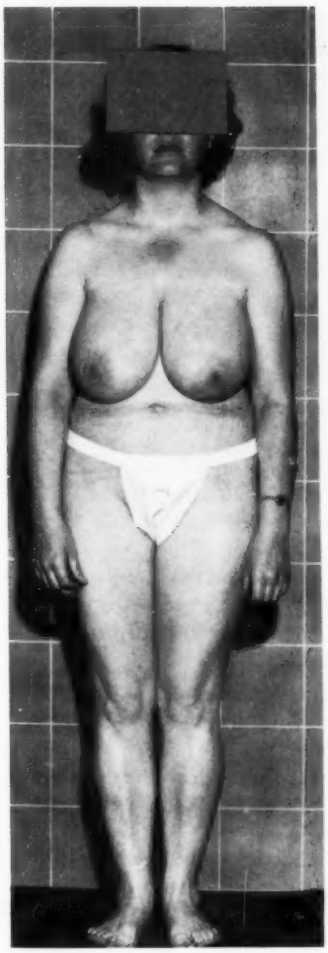

FIGURE 4. Patient with severe anterior pituitary failure.

the water test for primary or secondary adrenal failure.[4] In patients with adrenal failure, the administration of large amounts of water by mouth or in the form of intravenous solutions may lead to serious or even fatal water intoxication. This failure to excrete a water load in a normal fashion is corrected by the administration of cortisone or related steroids.

Although patients with anterior pituitary failure are pale and thereby may be suspected of having anemia, the levels of erythrocytes and hemoglobin in the blood are usually normal or only slightly decreased. In the presence of a tumor, the visual fields may show bitemporal defects, and roentgenograms of the skull may disclose enlargement of the sella.

Anorexia Nervosa

Although it has been stated that the differentiation of anorexia nervosa from anterior pituitary failure is so obvious that it is unnecessary to mention the former condition in discussions of pituitary disease,[5] the fact remains that patients with anorexia nervosa are all too frequently thought to have anterior pituitary failure. Thus there is often an un-

TABLE 1

CAUSES OF ANTERIOR PITUITARY FAILURE

I. Idiopathic failure

II. Secondary failure

A. Trauma
   1. Accidental
   2. Surgical

B. Neoplasm
   1. Primary
      a. Pituitary adenoma
      b. Craniopharyngioma
      c. Pinealoma
      d. Epidermoid
      e. Other tumors
   2. Metastatic

C. Vascular disease
   1. Postpartum necrosis (Sheehan's syndrome)
   2. Hemorrhage
   3. Thrombosis
   4. Aneurysm

D. Infectious disease
   1. Abscess
   2. Granulomatous diseases
   3. Meningitis

E. Systemic disease
   1. Sarcoidosis
   2. Xanthomatosis
   3. Leukemias, lymphomas and related diseases

necessarily long delay in beginning appropriate therapy in patients with anorexia nervosa.

Patients with advanced anorexia nervosa have what can be regarded as a partial, physiologic failure of the anterior pituitary gland as a result of starvation. Gonadotropins are no longer elaborated, and the menses cease. There may be a decrease in the urinary excretion of 17-ketosteroids and corticosteroids. The basal metabolic rate may be as low as minus 40 to minus 50, but despite this low basal metabolic rate most patients with anorexia nervosa have a normal level of protein-bound iodine and a normal uptake of radioiodine by the thyroid gland.

In general, laboratory data are not too helpful and, indeed, are not necessary in distinguishing anorexia nervosa from anterior pituitary failure. Differentiation can be made on the basis of a careful history, a physical examination, and the examiner's clinical impression. Patients with anorexia nervosa are almost invariably young females. While there may be some loss of sexual hair, these females rarely lose all of their axillary or pubic hair and actually may have a fine, lanugolike hair over the trunk. Most important is the fact that patients with anorexia nervosa, despite extreme emaciation, remain active and lead essentially normal lives—they continue to do their housework, carry on with their jobs, and, in the case of teen-agers, continue to do their schoolwork, go to dances, and keep up with their friends. On the other hand, patients with anterior pituitary failure who are ill enough to become emaciated are totally disabled and unable to do more than just exist. The finding of extreme emaciation in a young female who is mentally and physically active should suggest at once the presence of anorexia nervosa rather than anterior pituitary failure. Restoration of normal nutrition in these patients will restore the endocrine deficiencies without resort to hormonal therapy.

Etiology of Anterior Pituitary Failure

Anterior pituitary failure may be idiopathic, or it may arise secondary to lesions that damage the anterior pituitary gland or interfere with its blood supply. It has also become evident in recent years that some of the functions of the anterior pituitary gland, especially the release of gonadotropin, thyrotropin and adrenocorticotropin, are controlled by centers in the hypothalamus. Thus, lesions which invade the hypothalamus may cause failure of the anterior pituitary gland without encroaching on the gland itself.

The various causes of anterior pituitary failure are listed in table 1. Idiopathic failure is relatively rare and is usually seen in children, in whom it is responsible for some cases of pituitary dwarfism. Anterior pituitary failure in adults, on the other hand, is almost always secondary.

Trauma to the skull may damage the pituitary gland or alter its blood supply and lead to failure. Surgically induced failure of the adenohypophysis may be seen after operation for tumors in or near the sella, or failure may occur after hypophysectomy for the treatment

of metastatic carcinoma of the breast, diabetic retinopathy, malignant exophthalmos, and other conditions.

Because 75 to 100 patients with sellar, parasellar or suprasellar tumors are seen each year at the Mayo Clinic, the most common cause of anterior pituitary failure in our experience is tumor, the most common tumors being chromophobe adenomas and craniopharyngiomas. Eosinophilic adenomas, which cause acromegaly in adults, may also be associated with hypopituitarism, as may other tumors, such as the pinealomas, epidermoids, chordomas, gliomas, teratomas and metastatic tumors. Postpartum necrosis is the most common cause of anterior pituitary failure reported from other institutions.[6] Sheehan,[7] of Liverpool, England, has contributed so much to our knowledge of postpartum necrosis that anterior pituitary failure from this cause is known as Sheehan's syndrome. The condition occurs in women who have circulatory collapse at or shortly after the time of delivery. This results in necrosis of the anterior pituitary gland. The severity of the lesion may vary from patient to patient, and therefore all gradations of pituitary failure may result.

Conditions such as hemorrhage into the pituitary gland, thrombosis, aneurysm, meningitis or other infectious disease, sarcoid, xanthomatosis, leukemia and other diseases are occasional causes of hypopituitarism.

This list of causes is presented primarily to emphasize the fact that in the presence of anterior pituitary failure one should search for an underlying disease, because in most instances pituitary failure is not idiopathic. It must be remembered that normal visual fields and negative findings on neurologic examination and roentgenograms of the head do not rule out an intracranial lesion—we have seen a number of patients in whom anterior pituitary failure was present for months or years before other signs of the underlying lesion became evident.

Treatment

The treatment of patients with anterior pituitary failure has two parts. The first is correction of the cause of the failure if a tumor or some other condition amenable to treatment is found. Appropriate treatment may prevent permanent loss of vision or even loss of life. The second part of treatment is the use of hormones for the purpose of correcting endocrine deficiencies. In contrast to 10 years ago, today's endocrine treatment for adults with anterior pituitary failure is most effective.

The most important deficiency that requires correction is that of the adrenal cortices. Adequate replacement therapy is provided each day by administration of 20 to 30 mg. of cortisone orally in two or three divided doses.

In the event of severe stress, such as illness, surgery or accident, patients with anterior pituitary failure should be given additional adrenal support in the form of large doses of cortisone or related steroids. Administration of 200 mg. of cortisone or its equivalent each day will supply the needed support. If the stress can be anticipated, as in the case of an elective surgical procedure, the cortisone can be given intramuscularly. We usually give 200 mg. intramuscularly two days before the operation, and the same amount the day before and again on the morning of the procedure. The daily dose is reduced gradually over the next few days, and the patient is then given his usual daily maintenance dose by mouth. When the stress cannot be anticipated, it will be necessary to give the steroids by the intravenous route. In the event of minor illness, patients are advised to increase their daily dose of cortisone to 50 mg. a day, with the dose being reduced to the usual level as soon as the illness is over. Patients are cautioned to consult their physicians at once for the parenteral administration of cortisone in the event that nausea or vomiting prevents them from taking cortisone by mouth. Each patient should carry a card which gives his diagnosis and program of treatment.

Thyroidal deficiency is treated by giving 2 to 3 gr. of U.S.P. thyroid, or its equivalent, each day, unless there is some valid contraindication. In the presence of coronary arterial disease or other contraindication to starting with full replacement doses of thyroid, we give patients ¼ gr. of thyroid a day and gradually increase the dose over a num-

ber of weeks until the optimal daily dose is reached. Prior to the advent of cortisone, so-called adrenal crises could be precipitated by the administration of full doses of thyroid in the presence of adrenal insufficiency. We have yet to see a similar episode in patients with hypopituitarism who are given 20 to 30 mg. of cortisone each day at the time that the full daily ration of thyroid is begun.

Gonadal deficiency may be treated by the administration of androgens, in the case of men, and estrogens, in women, but whether such therapy is used depends on the age of the patient. We do not usually use androgenic therapy in elderly men or estrogenic therapy in women who are past the usual menopausal age. When androgens are used, we usually prefer the long-acting, intramuscular preparations rather than the oral preparations. Adequate replacement therapy is provided by 150 to 200 mg. of testosterone enanthate or testosterone cyclopentylpropionate given intramuscularly every three weeks. Patients who need this therapy are given instructions in the self-administration of these compounds.

For women who are in the premenopausal age group, we still advise the use of preparations that can be taken orally, such as diethylstilbestrol or PREMARIN®. We generally give 0.5 to 1.0 mg. of diethylstilbestrol or its equivalent each day for three weeks of each month. Since some patients occasionally experience nausea from the use of estrogenic substances, they are asked to take the medication at bedtime rather than in the morning.

With adequate replacement therapy, patients with anterior pituitary failure can lead practically normal lives. For this reason it is important to recognize the deficiency and to institute treatment at once.

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Diagnosis and Treatment of Congenital Virilizing Adrenal Hyperplasia

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The principle of treatment of congenital virilizing adrenal hyperplasia is to suppress adrenal activity with a cortisonelike steroid, thus preventing formation of precursors which have androgenic and sometimes hypertensive effects. After establishing a depot with initial large doses, the minimal maintenance dose for adequate suppression is determined by the output of urinary 17-ketosteroids. In growing children it is also important to regulate long-range treatment according to rates of growth and osseous development. Cortisone dosage must be greatly increased during periods of stress. In the author's opinion, most of the newer steroids advocated for therapy do not have an advantage over cortisone, desoxycorticosterone acetate or both.

LAWSON WILKINS

CUSHING'S syndrome is due to an overproduction of a normal pattern of adrenal steroids, of which the principal ones are hydrocortisone and corticosterone. In congenital virilizing adrenal hyperplasia there are inborn defects in the hydroxylating enzymes of the adrenal which normally convert progesterone into hydrocortisone, corticosterone and aldosterone.[1,2] These defects result in the accumulation of androgenic steroids and certain precursors. The androgens are responsible for the masculinization of the external genitalia which occurs in the female during fetal life and for the progressive virilization, accelerated growth and epiphyseal ossification which develop postnatally in both sexes.

There are, however, three different types of congenital virilizing adrenal hyperplasia, each of which is due to a different enzymatic defect. Of 113 patients whom we have studied, 66 had simple virilism without other symptoms (table 1). This type is due to a partial

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TABLE 1

TYPES OF VIRILIZING ADRENAL HYPERPLASIA

	VIRILISM ALONE	SALT-LOSING	HYPERTENSIVE	TOTAL
Females	54*	32	5	91
Males	12	8	2	22
	66	40	7	113

*Nine raised as males.

defect in C_{21}-hydroxylation. Forty of the patients, or about one-third, showed in addition a tendency to lose sodium. This disorder, if untreated, results in death. Such patients have a more complete defect of C_{21}-hydroxylation and also an inability to form aldosterone.[3] Seven patients had, in addition to virilism, hypertension which responded to suppression of adrenal activity with cortisone and which recurred when treatment was withdrawn. In this type of the disorder there is a defect of C_{11}-hydroxylation, leading to formation of 11-desoxyhydrocortisone (compound S) and desoxycorticosterone (DOC).[4] The desoxycorticosterone is believed to be the cause of the hypertension.

Diagnosis

Females—In females, the secretion of adrenal androgens during fetal life causes masculinization of the external genitalia but does not affect the ovaries or genital ducts. The masculinization consists of phallic enlargement, with or without labioscrotal fusion. This must be distinguished from ambiguous genitalia resulting from other conditions.[5] These include nonadrenal female pseudohermaphroditism, which usually is associated with administration of androgens or synthetic progestins to the mother during pregnancy,[6] male pseudohermaphroditism, true hermaphroditism, and certain atypical forms of gonadal dysgenesis. Accordingly, the diagnosis cannot be based on anatomic abnormalities but depends rather on the finding of levels of urinary 17-ketosteroids which are definitely elevated in respect to the patient's age (see table 2). Later there is progressive virilization with precocious appearance of sexual hair, excessive growth and musculature, and advanced epiphyseal development. One should remember also that occasionally in female pseudohermaphroditism the urogenital sinus opens at the tip of the phallus, and these individuals can readily be mistaken for cryptorchid males unless the chromatin pattern of the buccal smear is studied.

Males—The adrenogenital syndrome in males is distinguished from other types of sexual precocity due to early idiopathic activation of the pituitary or to hypothalamic lesions by the fact that the urinary 17-ketosteroids are elevated above the usual adolescent or adult level while the testes usually, but not always, remain small and immature.

Characteristics of various types—The hypertensive type of adrenal hyperplasia differs from the type in which there is simple virilization only in the occurrence of elevated blood pressure which responds to cortisone therapy and recurs when treatment is withdrawn.

Infants with the salt-losing type of adrenal hyperplasia usually present symptoms of anorexia, irritability, vomiting and weight loss in the first two or three weeks of life. Unless proper treatment is given, severe dehydration, circulatory collapse and death ensue rapidly. When salt-losing symptoms appear in a female pseudohermaphrodite, the true nature of the disorder is readily suspected; but in males death may occur before macrogenitosomia is obvious. The condition should be suspected when the history reveals that siblings have died with similar symptoms. Diagnosis depends on the finding of low serum sodium and carbon dioxide levels and, more importantly, elevated serum potassium. However, to prove that the sodium loss is due to virilizing adrenal hyperplasia and not to some other adrenal disorder, it is necessary to demonstrate elevation of the urinary 17-ketosteroid level.

Methods of Treatment

The principle of treatment of congenital virilizing adrenal hyperplasia is to suppress adrenal activity by supplying the physiologic requirements with a cortisonelike steroid, thus preventing the formation of precursors which

TABLE 2

EXCRETION OF 17-KETOSTEROIDS IN PATIENTS OF DIFFERENT AGES WITH UNTREATED ADRENAL HYPERPLASIA

AGE	NUMBER OF PATIENTS	17-KETOSTEROIDS (MILLIGRAMS PER DAY) IN UNTREATED PATIENTS	NORMAL VALUES FOR AGE GROUPS
0-6 mo.	19	1-10	0.5
7-12 mo.	2	3-10	0.5
1-5 yr.	28	4-30	1.0
6-9 yr.	9	11-40	2.0
10-15 yr.	6	16-50	10.0
15 yr.	12	21-80	15.0

have androgenic and sometimes hypertensive effects (figure 1). Infants with the salt-losing type usually require treatment with desoxycorticosterone or some other sodium-retaining hormone and an increased intake of sodium chloride in addition to cortisone.

Initially, to bring about rapid suppression of the abnormal adrenals, relatively large doses of cortisone are given, after which it is necessary to determine the minimal dose required to maintain adequate suppression. This determination is made by following the output of 17-ketosteroids, as illustrated in figure 2. In growing children it is equally important to regulate long-range treatment according to the rates of growth and osseous development (figure 3). If adrenal suppression is inadequate, osseous development continues to advance rapidly and will lead to premature epiphyseal fusion. If excessive treatment is given, growth and development will be retarded unduly. With proper dosage, growth proceeds normally and abnormal metabolic changes do not occur.

Table 3 lists the initial and maintenance doses of cortisone which we have found to be effective. It is most important to appreciate the differences between intramuscular and oral medications, which are based on the rates of absorption of the steroid. When cortisone acetate suspension is given intramuscularly, it is absorbed slowly and has an action extending over three or four days. After a depot has been established by giving daily injections for 5 to 10 days, doses spaced at intervals of three or four days will maintain a uniform level of suppression. Some workers have obtained satisfactory results with depot preparations that have a still longer action, such as the trimethyl acetate of prednisone.

When cortisone is given orally, it is absorbed rapidly and is effective for only a few hours. Accordingly, to maintain uniform adrenal suppression it is necessary to administer it three to four times daily, and at a dosage level approximately two or three times the daily intramuscular dose.

Some infants with milder degrees of the sodium-losing type of virilizing adrenal hyperplasia, when treated with cortisone, can be maintained in electrolytic balance by merely adding 2 to 5 gm. of sodium chloride to their daily diet, but most patients with this type of the condition need in addition a sodium-retaining hormone and are safer if it is given. We still prefer the implantation of 2 to 5 125 mg. pellets of DOCA®, adjusting the salt intake according to requirements. The pellets are absorbed gradually over a period of 9 to 12 months. At the end of this period our patients have not required reimplantation of pellets. In some cases the patients have been followed for as long as 10 years and have not had any difficulties when cortisone therapy was continued and extra salt was offered according to their desires. We have shown, however, that these patients, who seem to have lost their salt-losing tendency, still are unable to conserve sodium and get into trouble when their intake of salt is restricted.[3]

Instead of implanting pellets, some workers have preferred to give injections of long-

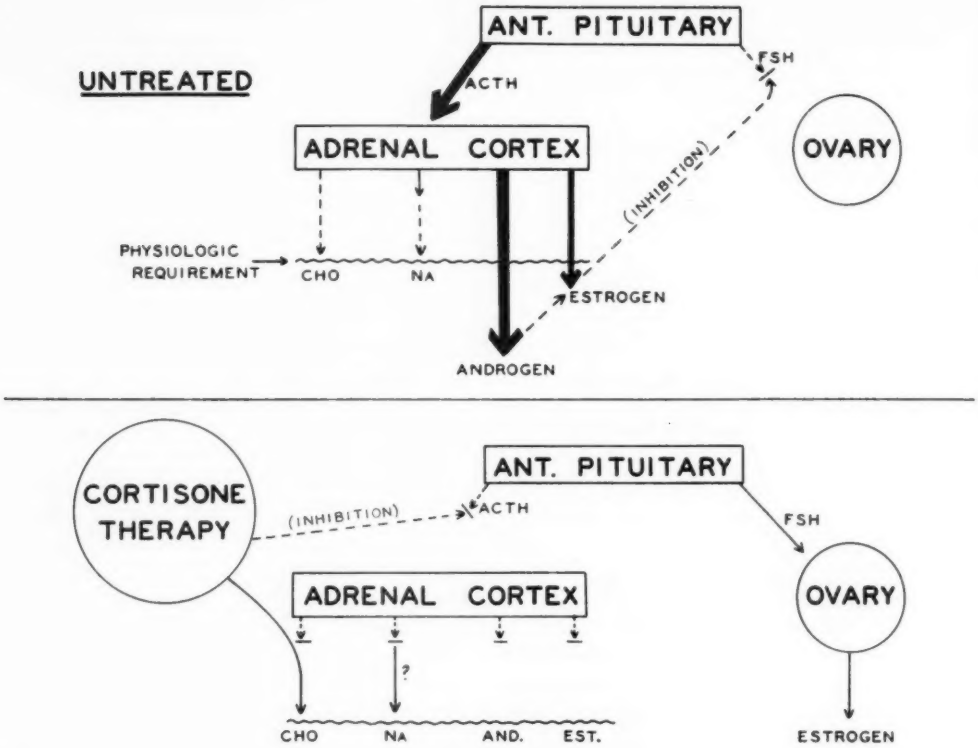

FIGURE 1. Action of cortisone in the treatment of virilizing adrenal hyperplasia.

Because of the partial impairment of the ability of the adrenal to convert progesterone into hydrocortisone and compound B, there is a relative deficiency of carbohydrate-regulating hormones (CHO) and an excessive production of both androgenic and estrogenic steroids. The estrogens produce no effect on the sex organs because they are antagonized by the excessive amounts of androgen. In order to meet the physiologic requirements for hydrocortisone, there is increased secretion of ACTH, causing hyperplasia of the adrenals and further increase in androgen and estrogen. The high concentration of circulating sex hormones inhibits the secretion of pituitary gonadotropins (FSH and LH) so that the gonad remains immature and does not secrete.

When cortisone is given in amounts to meet the physiologic requirements, ACTH is inhibited and the abnormal adrenal is put at rest except that it may continue to secrete aldosterone (Na). When the adrenal androgens and estrogens are suppressed, pituitary gonadotropin can be secreted to cause maturation of the gonads and secretion of the normal hormones of the ovary or testis. This activity of the pituitary depends on the attainment of a level of maturity corresponding to a *bone age* of adolescence (13 to 14 years).

acting trimethyl acetate of desoxycorticosterone at intervals of three to four weeks. It is, however, much more difficult to determine the amount and timing of doses in infants than in adults.

The 9α-fluoro- and 9α-chloro- derivatives of hydrocortisone have both adrenal-suppressive and sodium-retaining effects, and it was hoped that one of these drugs could be used as a single agent in the treatment of the salt-losing type of adrenal hyperplasia. Unfortunately, when 9α-fluorohydrocortisone was given in a dosage of 0.5 to 1 mg. per day, which is the amount necessary to suppress the 17-ketosteroids, it invariably caused hypertension and excessive retention of sodium. In combination with cortisone, 9α-fluorohydrocortisone in a dosage of 0.05 to 0.2 mg. can be used instead of Doca to control loss of sodium. A better, but not ideal, ratio of the two effects is provided by 9α-chlorohydrocortisone, and we have successfully treated a number of infants

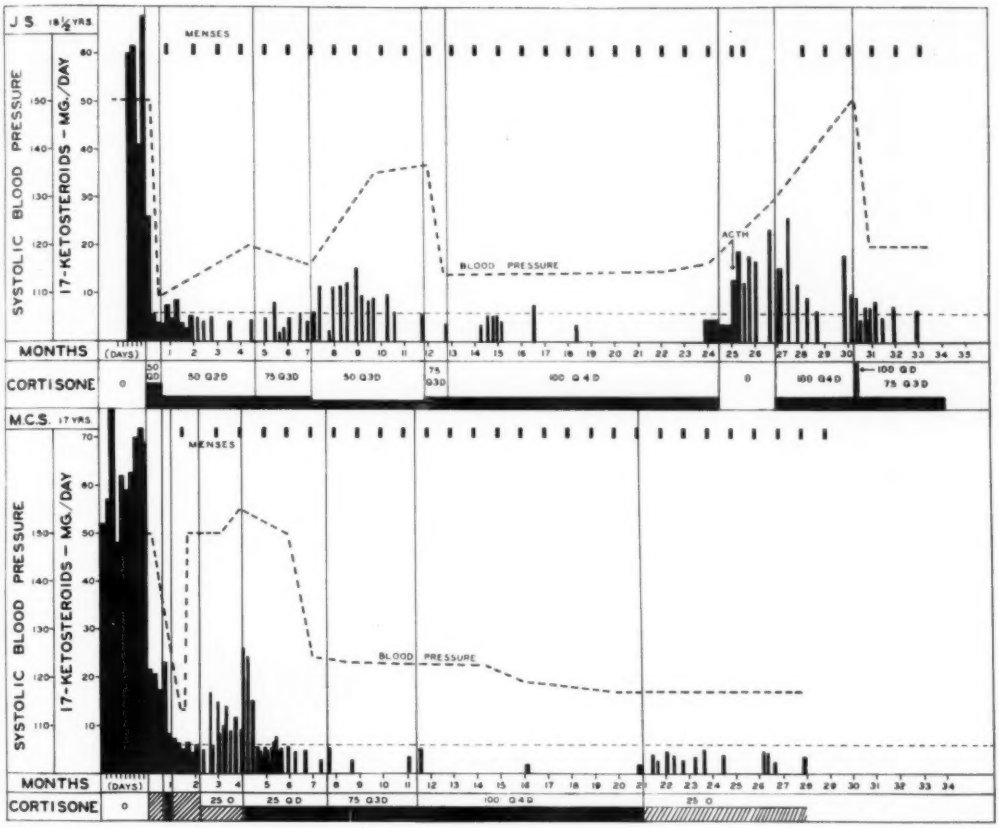

FIGURE 2. Method of determining minimal maintenance dose of cortisone for suppression of the adrenals by following the output of 17-ketosteroids.

In the case depicted in the upper part of the figure, 50 mg. of *intramuscular* cortisone daily reduced the output of 17-ketosteroids from 60 mg. to about 6 mg. per day. The dosage was then decreased to 50 mg. every second day, and then to 75 mg. every third day (equivalent to 25 mg. daily), with maintenance of 17-ketosteroid suppression. When the dosage of intramuscular cortisone was reduced further to 50 mg. every third day (equivalent to 16.6 mg. daily) the urinary 17-ketosteroid level rose to 10 to 12 mg. per day. The patient was subsequently maintained on 100 mg. every fourth day.

In the case depicted in the lower part of the figure, 50 mg. of *oral* cortisone daily given in divided doses did not reduce the output of 17-ketosteroids below 20 mg. per day. With a change in cortisone administration to 50 mg. given intramuscularly, the 17-ketosteroids fell promptly to 6 mg. per day. Subsequently, 50 mg. of oral cortisone maintained this level but 25 mg. orally was inadequate. Eventually the patient was maintained on intramuscular cortisone (equivalent to 25 mg. per day) for nearly two years. When the route of administration was again changed, to 25 mg. of oral cortisone, there was eventually an escape from suppression.

Both of these patients had the hypertensive type of virilizing adrenal hyperplasia. Blood pressure fell to normal levels when the adrenals were adequately suppressed but rose again when there was an escape.

with 5 mg. of this drug daily for as long as two or three years without ill effects. However, the drug is dangerous for general use. In our series of cases there has been one death associated with its use, that of a child who was maintained on 5 mg. chlorohydrocortisone and was mistakenly given 5 mg. of hydrocortisone for two days; the crisis which ensued was fatal in spite of emergency treatment with intravenous cortisone-hemisuccinate, salt and intramuscular Doca.

It should be emphasized most strongly that

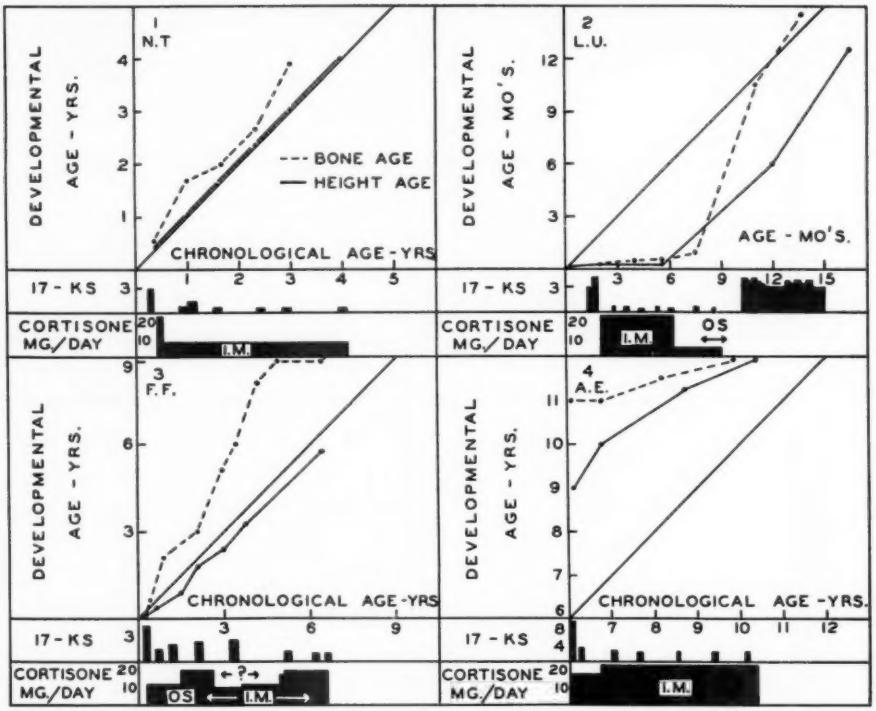

FIGURE 3. Rates of growth and osseous development as guides to optimal cortisone therapy.
Case 1. Satisfactory treatment. Normal growth and development.
Case 2. Excessive treatment. Suppression of growth and development during the first six months.
Case 3. Inadequate therapy. Excessive skeletal maturation.
Case 4. Excessive osseous development was inhibited for five years, during which period growth proceeded at a normal rate.

whenever the adrenals have been suppressed by any of the cortisonelike steroids they are unable to respond normally to the increased needs for hydrocortisone in conditions of stress, such as acute infection, trauma or surgical operation. The parents and attending physician must be warned that under these circumstances greatly increased amounts of cortisone must be given. If there is time to prepare for an operation, the additional cortisone may be given intramuscularly beginning three days preoperatively. In an emergency it should be given orally or intravenously because of its more rapid action by these routes.

Table 4 lists some of the newer steroids which have been advocated for therapeutic use and compares their adrenal-suppressive activity with that of oral cortisone and their salt-retaining activity with that of Doca given intramuscularly. The enhanced potency and prolonged activity of the newer orally administered derivatives of cortisone probably depend at least in part on decreased rates of degradation. In our opinion most of these drugs do not have advantage over cortisone or Doca or both in the treatment of virilizing adrenal hyperplasia.

Prednisone and prednisolone are about five times as potent as oral cortisone and probably have a more prolonged action, as they can be given once or twice daily instead of three or four times a day. The fact that they have less salt-retaining action is not advantageous for our present purpose, as we do not encounter excessive retention of salt with the small doses of cortisone we employ.

TABLE 3

INITIAL AND MAINTENANCE DOSAGES OF CORTISONE IN TREATMENT OF VIRILIZING ADRENAL HYPERPLASIA

AGE (YEARS)	17-KETOSTEROIDS (MILLIGRAMS PER DAY)		CORTISONE DOSAGE (MILLIGRAMS)		
	Before treatment	*Under treatment*	*Initial (intramuscular)*	*Maintenance*	
				Intramuscular	Oral
Over six	20-80	4-6	100 per day	75 every three days (equal to 25 per day)	25 two to three times a day (equal to 50 to 75 per day)
Two to six	8-20	2-4	50 per day	50 to 75 every three days (equal to 16 to 25 per day)	12.5 to 25 two to three times a day (equal to 25 to 50 per day)
Under two	2-8	0.5-1.5	25 per day	25 to 37.5 every three days (equal to 8 to 12 per day)	5 to 10 three to four times a day (equal to 15 to 20 per day)

Triamcinolone is considerably more potent than advertised and has at least 10 times the adrenal-suppressive effect of cortisone in our cases. We have encountered undesirable effects such as generalized hypertrichosis, weight loss, psychotic symptoms and papilledema.

Dexamethasone has a high degree of potency, perhaps 50 or more times that of cortisone, and we have seen flagrant Cushing's symptoms when the dosage was calculated according to the potency advertised.

Another very potent drug is 9α-fluoroprednisolone ($\triangle^1$FF), and it has a dangerously high salt-retaining activity.

We believe that these very potent drugs have no real place or advantage in therapy. They are, however, interesting and useful tools in the scientific investigation of steroid patterns, because the amounts required for adrenal suppression are so small that their metabolites do not contribute anything to the urinary steroids.

The halogenated steroids, 9α-fluorohydrocortisone and 9α-chlorohydrocortisone, have both adrenal-suppressive and strong salt-retaining effects, and I have already mentioned their possible use in the salt-losing type of adrenal hyperplasia.

Results of Treatment

We have now treated 96 patients with cortisone or related steroids for periods ranging

TABLE 4

COMPARISON OF SOME THERAPEUTIC STEROIDS

DRUG	ROUTE	SUPPRESSIVE	SODIUM-RETAINING
Doca	Intramuscular	0	1
Cortisone (E)	Oral	1	0.03
Prednisone ($\triangle^1$-E)	Oral	5	0.03
Triamcinolone (160H$\triangle^1$FF)	Oral	10	—
Dexamethasone (16CH$_3\triangle^1$F)	Oral	50-100?	—
Chlorohydrocortisone (9αClF)	Oral	4	0.2
Fluorohydrocortisone (9αFF)	Oral	12	10-15
Fluoroprednisolone (9α$\triangle^1$FF)	Oral	40	3?
Aldosterone	Oral	0.3	25

TABLE 5

AGES OF PATIENTS AT BEGINNING OF CORTISONE THERAPY, AND DURATION OF TREATMENT

AGE	FEMALES	MALES	TOTAL
Less than two years	38	4	42
Two to 10 years	21	14	35
11 to 18 years	9		9
19 to 49 years	10		10
	78	18	96

DURATION OF TREATMENT	CASES
Five to 10 years	58
Two to five years	24
Less than two years	14
	96

from a few months to more than 10 years (table 5). Since the amounts of steroid necessary to maintain suppression of the abnormal adrenals are approximately the same as those secreted by the normal adrenals in health, abnormal metabolic effects are not observed.

The earlier in life that treatment is begun, the more satisfactory are the results. Most of the infants who were treated before the age of two years did not have pubic hair; if a small amount had developed, it disappeared when treatment was given. They have grown and developed in an entirely normal manner, and epiphyseal development, which was a number of years advanced in some instances, has been held in check. At this writing, none of the patients have shown puberal development. Surgical correction of the external genitalia usually has been carried out in females before the age of two or three years.

In the cases in which treatment was begun between the ages of 2 and 10 years, progressive virilization with increasing pubic hair and sometimes acne already had occurred. Epiphyseal development usually was far advanced. Therapy checked the rapid progress of epiphyseal development, preventing too much stunting of growth, but usually full adult height was not attained. Progressive virilization was checked, and acne and hirsutism disappeared. If the bone age was less than 11 or 12 years at the time cortisone therapy was begun, the patient continued to develop at a normal rate; a number of years elapsed before there was a gradual onset of adolescence with normal sexual development corresponding to the true sex. If, however, the osseous development had reached the level of 13 or 14 years before treatment was begun, there was an abrupt onset of adolescent sexual development irrespective of the chronologic age. The girls showed rapid feminization with

TABLE 6

MORTALITY IN DIFFERENT TYPES OF VIRILIZING ADRENAL HYPERPLASIA

	SIMPLE VIRILISM		SALT-LOSING		HYPERTENSIVE		ALL TYPES	
	Total cases	*Deaths*	*Total cases*	*Deaths*	*Total cases*	*Deaths*	*Total cases*	*Deaths*
Treated	54	1	36	6	6	1	96	8*
Untreated	12	0	4	4	1	0	17	4

*An analysis of these eight deaths reveals the following:

Type	*Duration of treatment*	*Type of death*
Virilism	15 months	? Fever, convulsions, 24 hours
Salt-losing	34 months	? Fever, convulsions, 24 hours
	3 months	? Fever, cyanosis, dyspnea, 24 hours
	24 months	Withdrawal of chlorohydrocortisone
	2 weeks	Hypernatremia, excess sodium chloride; chlorohydrocortisone
	3½ months	? Vomiting, collapse, cardiac failure
	22 months	Influenzal encephalitis?, respiratory failure
Hypertensive	39 months	Unrelated neurologic disorder

breast development and the onset of menstruation and ovulation within a few months. In boys the testes matured rapidly and spermatogenesis occurred. Because of the elaboration of testicular androgens, the 17-ketosteroid level rose and the patients continued to show progressive secondary sexual changes of normal male adolescence.

When treatment was instituted between the ages of 11 and 18 years, epiphyseal fusion usually had already occurred and further growth could not be expected. The girls feminized with remarkable rapidity. Features and body contours became more feminine. Acne and seborrhea disappeared. There was a slow, gradual decrease of hirsutism. At this age most of the female pseudohermaphrodites adjust well psychologically and treatment is exceedingly worthwhile. One cannot expect much from treatment of males at this age, because virilism continues to progress under the influence of testicular androgen. It is questionable whether any therapy is indicated except from the standpoint of bringing about fertility.

We have treated 10 women between the ages of 19 and 49 years. Two had had some breast development and scanty menses before treatment. Even at these ages, very satisfactory feminization occurs in most cases. When heavy beards have been present for years, shaving has had to be continued. Three of the 10 patients are married, and one has had a miscarriage. Three others are very maladjusted psychologically.

A special problem arises in the treatment of female pseudohermaphrodites who have been reared as males to an age at which a change of sex seems psychologically hazardous. We encountered nine such cases. In two the external genitalia appeared entirely male, with the urogenital sinus opening on the tip of the glans. Treatment with cortisone is desirable before adolescent age to prevent early virilization, excessive growth and premature epiphyseal fusion. When cortisone is given, however, it is most important to perform ovariectomy and hysterectomy to prevent future feminization with breast development and menstruation.

In young males, cortisone therapy is indicated the same as it is in females for the purpose of delaying precocious virilization and excessive growth, which would make the patient conspicuous among his playmates, and to avoid premature epiphyseal fusion, which would prevent attainment of normal adult height. When growth has ceased and testicular maturation is complete, the only reason for continuing cortisone therapy would be to maintain fertility. Although it is possible that the recurrence of the secretion of large amounts of adrenal androgens after cessation of treatment might inhibit gonadotropins and spermatogenesis, we have not observed this effect in several boys who have now been without treatment for three years.

Fatalities—Eight deaths have occurred among 96 patients under treatment (table 6). Six of these eight patients had the salt-losing type of adrenal hyperplasia. One death was due to a neurologic disorder and was in no way associated with the adrenal disorder or its treatment. In another case a fatal sodium-losing collapse resulted from the mistake of giving 5 mg. of hydrocortisone daily for two consecutive days to a patient who had been receiving 5 mg. of chlorohydrocortisone daily. A third death may have been caused by hypernatremia due to excessive administration of salt while the patient was receiving chlorohydrocortisone. The other five deaths are unexplained.

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The Proper Choice of Oral Antihyperglycemic Therapy in Diabetes Mellitus

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Insulin therapy can be completely replaced by oral antihyperglycemic therapy in most cases of ketoacidosis-resistant diabetes, i.e., those in which total deprivation of exogenous insulin does not, by itself, precipitate ketoacidosis. In the other major type of diabetes mellitus, termed ketoacidosis-prone, deprivation of exogenous insulin will, by itself, precipitate ketoacidosis, and total replacement of insulin therapy is not possible with the agents available at present; the oral agents have been used in these cases as adjuvants to insulin therapy, but in the authors' experience, they have been disappointing.

THE recent advances in the therapy of diabetes mellitus have engendered a growing uncertainty among clinicians as to the proper choice of therapy from among the abundance of regimens available. The purpose of this paper is to offer a reasonable and practical plan for making such decisions on the basis of current physiologic and clinical concepts of the disease. This will require (1) re-evaluation of the objectives of therapy, (2) classification of the disease along physiologic lines, and (3) consideration of the various regimens in terms of therapeutic effectiveness, safety and physiologic reasonableness. The conclusions expressed are naturally tentative and seem to fit both the available experimental data and our personal clinical experience, which we have reported in detail elsewhere.[1]

Objectives of Therapy

Therapy of diabetes mellitus today must be regarded as antihyperglycemic rather than antidiabetic, since there is no *conclusive* proof that "good control" protects against the specific vascular lesions of the disease. Nevertheless, inasmuch as it is unlikely that complete, hour-to-hour perfection in control of blood glucose concentration ever has been attained in overt diabetes, one cannot exclude the possibility of a relationship between hy-

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perglycemia and vascular "complications." For this reason, until such a relationship is excluded, current preoccupation with obtaining normal levels of blood glucose seems justified, *provided no risk of serious hypoglycemia or toxicity is thereby imposed.*

The prerequisites of an acceptable antihyperglycemic regimen must therefore be (1) antihyperglycemic effectiveness and (2) complete safety. A further consideration is that the antihyperglycemic action of the regimen should be achieved in a physiologically reasonable manner in respect to the presumed physiologic defect.

At the time of this writing, there are three oral antihyperglycemic agents available commercially. Two of them, tolbutamide (ORINASE®) and chlorpropamide (DIABINESE®), are sulfonylureas, and the third, phenformin (DBI), is a biguanide. Combined sulfonylurea-biguanide therapy may be considered as a fourth oral regimen, since it differs in many respects from therapy with either sulfonylurea or biguanide alone.

In selecting the regimen best suited to the individual diabetic patient, it is necessary first to classify the patient as to the type of diabetes.

Classification of the Disease

The two major categories of diabetes mellitus usually are designated by terms which refer either to the age of onset or to the stability of the blood glucose level and which, for this reason, can be misleading on occasion. We prefer to apply the term "ketoacidosis-resistant" to the group usually designated as "adult," "maturity-onset" or "stable." This group can be defined as comprising those patients in whom the total deprivation of exogenous insulin *does not, by itself,* precipitate ketoacidosis. Similarly, we prefer the term "ketoacidosis-prone" to the adjectives "juvenile," "growth-onset" and "labile," and apply it to those patients in whom deprivation of exogenous insulin *will, by itself,* precipitate ketoacidosis.

Ketoacidosis-resistant diabetes is characterized physiologically by the presence of insulin or insulinlike activity both in the beta cells and in the blood, often in amounts which are near normal, normal or above normal. Although the apparent paradox of hyperglycemia in the presence of normal insulin concentration has been explained in several ways, there is good reason to believe the basic functional lesion is a lowered beta-cell output of insulin in response to a given level of stimulation by the blood glucose concentration. Thus, whereas a normal beta cell might secrete a given quantity of insulin per minute at a blood glucose level of 80 mg. per cent, a level of 180 mg. of glucose might be required in ketoacidosis-resistant diabetes in order to stimulate the secretion of a like amount of insulin per minute. According to this concept, although the level of insulin in a patient with ketoacidosis-resistant diabetes is normal, it is normal only *because of* the high concentration of glucose.

Another theory which would explain the high insulin concentrations found in many patients with ketoacidosis-resistant diabetes invokes the idea of interference with insulin effect on glucose uptake in the tissues. Such interference might be the result of a metabolic lesion in the target cells or of insulin neutralization or destruction at any point between the beta cell and the target cells. Due to lack of definite evidence of the existence of an extrapancreatic defect, we favor the first theory.

Ketoacidosis-prone diabetes, by contrast, appears to be the result of an absolute insulin deficiency, since only negligible amounts of insulin activity have been demonstrated in the pancreas and in the blood in these cases. In this form of the disease the beta cells can be considered to be functionally inert.

Therapy in Ketoacidosis-Prone Diabetes

Because the ketoacidosis-prone patients are by definition lacking in endogenous insulin, such patients are completely dependent on exogenous insulin. Discontinuation of insulin therapy will therefore precipitate ketoacidosis. In this form of the disease, then, the oral agents can be used *solely* in an adjuvant role, the objective being to provide greater stability of control than is obtainable with insulin alone. The oral antihyperglycemic agents

should *never* be used for the total replacement of insulin in patients with ketoacidosis-prone diabetes.

Sulfonylureas—There is abundant evidence that the sulfonylureas exert their effect by causing an increase in the output of insulin by the beta cells.[2-5] In ketoacidosis-prone diabetes, however, the beta cells are functionally inert, and there is no evidence that administration of a sulfonylurea will resurrect them. Claims have been made in support of an ameliorating effect of Orinase and Diabinese as a supplement to insulin therapy, but the data are unconvincing. From our own experience, we feel that these agents are without significant effect and do not have a place in the treatment of ketoacidosis-prone diabetes.

Biguanide—The hypoglycemic action of DBI is not mediated through the beta cells. The mechanism of its action is still uncertain but is thought to take place in the extrapancreatic tissues. Many investigators have reported that supplementing insulin therapy with DBI has helped to stabilize labile diabetes. Our experience in this regard has, in general, been disappointing, but we continue to use the drug on a trial basis in the problem cases in which insulin alone fails to bring about satisfactory control. In our view, however, the problems of treatment of ketoacidosis-prone diabetes have not been changed materially by the advent of oral agents.

Therapy in Ketoacidosis-Resistant Diabetes

Sulfonylureas—The oral antihyperglycemic agents are valuable only in ketoacidosis-resistant diabetes, i.e., in patients who can produce endogenous insulin. In this form of the disease, the use of beta-cell stimulants such as the sulfonylureas provides a therapeutic approach which is attractive from the physiologic standpoint. It is our belief at present that every ketoacidosis-resistant patient should have a trial of sulfonylurea therapy.

Which of the two sulfonylureas, Orinase and Diabinese, should be used? Orinase is an extremely safe agent with a toxicity comparable to that of aspirin. It is short-acting, having a half-life of approximately four hours and being inactivated rapidly by the liver. This fact may explain the rarity of severe hypoglycemia during therapy with Orinase. As for its effectiveness, in approximately 35 per cent of ketoacidosis-resistant patients control can be achieved with mean fasting blood glucose levels in the normal range, and in 68 per cent control can be achieved with mean fasting blood glucose levels below 175 mg. per cent.[6] In the remaining patients, Orinase therapy produces little or no effect and the cases are classified as "primary failures."

Certain patients who are responsive to Orinase initially may become unresponsive after a variable period. The majority of these "secondary failures" are the result of dietary indiscretion or worsening of the diabetes due to infection or other stress.

Chlorpropamide (Diabinese) is a long-acting sulfonylurea which is excreted rather than inactivated. Consequently its half-life is five or six times as long as that of Orinase, which accounts at least in part for its greater "potency" on a weight basis. The advantages of its sustained action are offset by a greater risk of hypoglycemic reactions.[7-13] These reactions may be quite insidious and if unrecognized may lead to serious neurologic symptoms. This danger is an important although avoidable hazard of chlorpropamide therapy.

An additional hazard is the fact that chlorpropamide has been involved in serious hepatotoxic reactions of the cholestatic type.[7,8,10] In our experience, approximately 20 per cent of patients receiving chlorpropamide have had at least transient elevation of alkaline phosphatase concentration, and in a few instances alarmingly high values were encountered.[1] Dermatologic and hematologic disturbances also have been reported in patients receiving chlorpropamide.[7-13]

In view of the increased hazard of chlorpropamide therapy, what advantage, if any, does it provide over Orinase therapy, in terms of antihyperglycemic effectiveness? In an attempt to determine this, we substituted chlorpropamide for Orinase in cases classified as primary and secondary "failures" of Orinase therapy, which had been inadequately controlled with 3 gm. per day. In only about 12

TABLE 1

COMPARISON OF FOUR ORAL ANTIHYPERGLYCEMIC REGIMENS

AGENT	MECHANISM OF ACTION	ANTIHYPERGLYCEMIC EFFECTIVENESS	HYPOGLYCEMIC REACTIONS	TOXICITY
Orinase	Enhances secretion of endogenous insulin by beta cells	35 per cent of ketoacidosis-resistant diabetics can be controlled with mean fasting blood glucose levels of less than 120 mg. per cent, 68 per cent controlled with mean fasting blood glucose levels of less than 175 mg. per cent	Rare; occur in liver disease, in very old persons, and in patients who are taking salicylates	Rare minor reactions only
Diabinese	Same as Orinase	Same as Orinase, but will control about 12 per cent of Orinase "failures"	Not rare; a definite hazard. May be severe	Serious hepatotoxicity and dermatologic and hematopoietic reactions have occurred
DBI	Extrapancreatic site of action; mechanism unknown, possibly oxidative phosphorylation inhibition	Controls most Orinase-responsive diabetics and 26 per cent of Orinase "failures"	Not known to occur	No known toxicity; gastrointestinal symptoms only
Orinase-DBI combination	Probably a summation of Orinase and DBI actions, but synergism is a possibility	Controls 70 per cent of Orinase failures and 60 per cent of DBI failures	Not rare; a definite hazard. May be severe	Summation of Orinase and DBI toxicity

per cent of these tolbutamide-unresponsive patients did chlorpropamide therapy result in a significant improvement in control.[1]

Although other workers have had higher salvage rates,[9] we believe at present that it is difficult to justify the hazards of chlorpropamide therapy, uncommon though these may be, for the purpose of manipulating the blood sugar level. The final decision as to the place of chlorpropamide therapy should be deferred, however, pending the results of large-scale double-blind studies now in progress.

Biguanide—The mechanism of action of phenformin or DBI, the only biguanide now being used, is still a controversial matter. Although some workers have opposed its use for this reason, several years of experience with the drug have not indicated that phenformin-induced euglycemia is in any detectable way detrimental to diabetic patients. Its effectiveness as a blood sugar-lowering agent is impressive in most Orinase-responsive patients and in 26 per cent of patients who do not respond adequately to Orinase. As for its toxicity, to our knowledge no proved instance of organic disease resulting from DBI therapy has been recorded.

The side effects of DBI are limited to the gastrointestinal tract, and their incidence can be reduced by skillful use of the drug. Nausea, vomiting and diarrhea appear to be related to individual tolerance rather than to the dosage level, much as is the case with digitalis therapy. In rare instances we have encountered a patient unable to tolerate as little as 50 mg. of DBI, and we have had other patients who have taken more than 400 mg. of the drug daily without anorexia. To avoid gastrointestinal symptoms, it is recommended that a low dosage, e.g., 50 mg. per day, be given initially. Dosage can be increased each week by 25 mg. until either a therapeutic effect or evidence of toxicity appears. Although the manufacturer of the drug does not

recommend the use of dosages in excess of 150 mg. per day, the majority of patients in our clinic take considerably more than this amount. For each patient, dosage can be carefully titrated as to tolerance. The first sign of impending intolerance to DBI is an unpleasant metallic taste; anorexia usually follows. Ordinarily the appearance of these symptoms does not necessarily warrant a cutback in dosage, but they should signal caution in respect to further increase in dosage. Perhaps because of its mild anorectic effect, DBI is the only one of the antihyperglycemic substances, including insulin, unassociated with the problem of weight gain. The possible usefulness of DBI in the treatment of obesity, nondiabetic as well as diabetic, deserves careful study.

A notable advantage of DBI is that it is not by itself a cause of hypoglycemia.

Combination therapy—Combination therapy[14,15] with Orinase and DBI is considered as an entirely separate regimen because it differs in many important respects from therapy with either agent alone. First, it surpasses all other oral regimens in antihyperglycemic effectiveness.[1] Seventy per cent of both primary and secondary tolbutamide failures and 60 per cent of all DBI failures have been successfully controlled by means of Orinase-DBI combination therapy, a salvage rate not approached by any other oral agent.[15]

Hypoglycemia, which is never encountered in therapy with DBI alone and which is observed infrequently in therapy with Orinase alone, is a problem in combination therapy, just as with insulin therapy or Diabinese therapy. However, the toxicity of combination therapy is no greater than that of either Orinase or DBI therapy.

In general, combination therapy is used only in patients who cannot be controlled adequately by Orinase or DBI alone. Most such patients have been receiving tolbutamide for three or more weeks in a dosage of 3 gm. daily. This dosage level of tolbutamide is continued without change, and DBI is added in the manner described previously until adequate control or intolerance to DBI occurs.

For patients who fail to respond adequately to combination therapy, insulin therapy is, of course, instituted. We estimate, however, that adequate control has been maintained in close to 90 per cent of *all* ketoacidosis-resistant patients with oral therapy alone, using one of the foregoing regimens.

Table 1 is a comparison of the four antihyperglycemic regimens discussed.

Summary

The advent of oral antihyperglycemic therapy has facilitated the regulation of blood glucose in a large segment of the diabetic population. The principal beneficiaries have been the ketoacidosis-resistant patients, in the vast majority of whom insulin therapy can be completely replaced by one or another of the currently available oral regimens.

Considering the goals of therapy as outlined, Orinase is at present the drug of choice in ketoacidosis-resistant patients, meeting the requirements of antihyperglycemic effectiveness, safety and physiologic reasonableness. In a considerable number of patients who initially or eventually fail to respond to Orinase, DBI therapy may produce the desired control of blood glucose, either alone (in 26 per cent) or used in combination with Orinase (in 70 per cent).

For the ketoacidosis-prone category of diabetic patients, total replacement of insulin therapy by any of the available agents is, of course, not possible. All these drugs have, however, been employed as adjuvants of insulin therapy, the objective being to stabilize labile diabetes. In our view, only DBI is of any value for this purpose, and in our experience this stabilization has been achieved in only a disappointingly few truly labile patients.

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MEETINGS *and Postgraduate Courses*

American College of Allergists, Dallas: Graduate instructional course and annual congress, March 12-17, at the Statler Hilton. For further information, write to: Dr. John D. Gillaspie, Treasurer, 2141 14th Street, Boulder, Colorado.

American College of Physicians: Postgraduate courses to be presented in 1961:

Selected topics in internal medicine, University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, February 20-24

Internal medicine: Selected subjects, McGill University Faculty of Medicine, Montreal, March 13-17

Advanced clinical electrocardiography, University of Tennessee College of Medicine, Memphis, March 20-24

Endocrinology and metabolism, University of Virginia School of Medicine, Charlottesville, March 23-25

Problems of growth and aging, Lankenau Medical Building, Philadelphia, April 12-15

Gastroenterology, University of Pennsylvania School of Medicine, Philadelphia, May 15-19

Current aspects of internal medicine, State University of Iowa College of Medicine, Iowa City, June 19-23

For further information, write to: American College of Physicians, 4200 Pine Street, Philadelphia 4.

New York University Medical Center, New York: Postgraduate course in surgery of the hand to be held March 6-11. For further information, write to: Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16.

University of Maryland School of Medicine, Baltimore: Postgraduate course in advances in medical science, which began in January, will continue through May 24. For further information, write to: Postgraduate Office, University of Maryland School of Medicine, 522 West Lombard Street, Baltimore 1.

University of Texas M. D. Anderson Hospital and Tumor Institute, Houston: Annual symposium on fundamental cancer research, "The molecular basis of neoplasia," February 23-25. For further information, write to: Publications Department, University of Texas M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston 25.

The Women's Medical Association of the City of New York: The Mary, Putnam Jacobi Fellowship, offered to a graduate woman physician, American or foreign, will begin October 1, 1961, for one year. The fellowship is given for medical research, clinical investigation or postgraduate study in a special field of medicine. Applications must be filed before March 1. For further information regarding the stipend and qualifications of candidates, write to: Dr. Ada Chree Reid, Chairman, 118 Riverside Drive, New York 24.

Classification, Diagnosis and Treatment of Hypothyroidism

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Hypothyroidism is discussed under the headings of myxedema, permanent hypothyroidism without myxedema, and cretinism. The accuracy and limitations of various laboratory tests of thyroid function are reviewed in relation to these categories. Three features which may be useful in recognition of atypical cases are abnormal menstruation, psychosis and anemia.

Treatment consists of continual replacement therapy with desiccated thyroid. In cretinism, although normal function seldom is attainable, the physician should attempt to obtain maximal benefit for the patient.

RICHARD GOLDSMITH

THE field of endocrinology is still partly composed of vague forms and ideas, and this is often thought to be particularly true in regard to hypofunction of the thyroid. Yet in recent years there has been more fruitful widening of clinical horizons in the area of thyroid disease than in almost any other. The probable reason for this paradox is widespread misunderstanding of the basic concepts of hypofunction of the thyroid gland. Therefore, the purpose of this article is to review briefly these concepts.

Classification of Hypothyroidism

It is appropriate for purposes of this discussion to divide the clinical syndromes related to hypofunction of the thyroid gland into three main groups: myxedema, permanent hypothyroidism without myxedema, and cretinism.

Myxedema—The largest group is the category of myxedema, which refers to the constellation of signs, symptoms and laboratory alterations that is seen inevitably in all patients with athyreosis. Total absence of thyroid tissue may result from therapeutic ablation of the gland actually or functionally, from idiopathic atrophy, from destruction of the

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gland by another disease process, or from glandular atrophy secondary to underproduction of thyrotropin by the anterior pituitary. All the various facets of this syndrome are not always seen together in the early stages, even though in time all do become apparent. The disease should be considered as a permanent, end-result phenomenon.

While most clinicians are quite familiar with the syndrome of myxedema, certain aspects of the symptomatology are confusing. For example, a patient can be hypertensive and nervous and can have tachycardia and still not have any functioning thyroid to speak of. The secretory products of the thyroid gland are not necessary for any specific function performed by the body. Rather, these products are essential for the effective functioning of many of the complex interrelated biologic systems operating within the human body. Obviously, then, these secretory products are not the sole controlling factors in the regulation of, say, vascular tone, cardiac rate and rhythm, and the rate of transmission of synaptic impulses. Bearing in mind these fundamental physiologic considerations, it is obvious that the diagnosis of myxedema is not invalidated by the presence or absence of any particular symptom or sign.

Complicating any clinical interpretation of the syndrome is its gradual development; often the syndrome is apparent only a number of years after the first signs of hypothyroidism appear. This slow evolution may introduce considerable doubt as to the existence of the syndrome, even though much of the picture is typical.

Permanent hypothyroidism without myxedema—The second group is, to say the least, a relatively small one. As a rule, most patients in whom hypofunction of the thyroid gland develops will, in the course of their lives, progress to complete athyreosis and eventual myxedema. However, a few patients demonstrate what appears to be permanent incomplete hypothyroidism without any progression to athyreosis. Some of them are born with congenitally defective thyroid glands, and some acquire thyroid defects postnatally. Such defects are biochemical in nature and place the thyroid gland at a biologic disadvantage. As a result, the thyroid gland usually works with maximal efficiency considering the existing defect. This means it usually becomes hyperplastic. But, in spite of a hyperplastic response, the patient still may have a net undersupply of normal thyroid secretory products and therefore appear hypothyroid. Such a patient always has some thyroid tissue and usually has a goiter. There is reason to believe that biochemical defects of such a nature are being produced as a result of irradiation therapy to the thyroid gland for hyperthyroidism, but it is probably too early to say whether or not the partial hypothyroidism seen in such patients after irradiation therapy is indeed permanent without progression to myxedema or regression to euthyroidism. Finally, some patients with hypopituitarism fit in the category of permanent partial hypothyroidism.

Cretinism—The third category of hypothyroidism is cretinism. Originally this term was used to describe only those unfortunate persons who were born with evidence of developmental retardation in utero as a result of absent fetal thyroid function. Such persons may go through life with all the usual disabilities accruing to the myxedematous person in addition to the congenital abnormalities.

Formerly, if a goiter was not visible at the time of birth, the diagnosis was considered to be "sporadic cretinism." If a goiter was visible at the time of birth (and this was believed to happen only in areas endemic for goiter and in families in which other members demonstrated goiters), the diagnosis was considered to be "endemic cretinism." In recent years, however, it has become evident that a few persons not living in such endemic areas are born with visible goiters and with less obvious display of intrauterine deprivation of normal circulating thyroid secretory products than is usual in cretinism. There usually is a history of consanguinity. After birth, myxedema may develop and continue to be demonstrated. However, some of these persons, because of effective compensatory hyperplasia of the thyroid, eventually become euthyroid or even hyperthyroid. Thus, the second and third categories of this classifica-

tion of hypothyroidism overlap and are separable only for purposes of discussion.

In this classification, no mention has been made of a clinical syndrome of nongoitrous, spontaneous partial hypothyroidism sometimes referred to as "metabolic insufficiency." Some workers believe that such a disease exists as a nonprogressive, permanent state of "limbo." Except for studies involving the patients in the second and third groups of the classification just presented, there is absolutely no binding evidence of the existence of permanent partial hypothyroidism.

Diagnosis

Today, as always, diagnosis of any of these syndromes depends first on clinical suspicion. However, today this suspicion can and always should be reinforced by some form of laboratory confirmation.

Frank end-stage myxedema seldom presents any difficulty in differential diagnosis, but even in these cases the etiologic basis of the disease may not be obvious. If a patient has undergone treatment for hyperthyroidism previously, the cause is evident. If a patient has a goiter, again the problem probably lies within the thyroid gland as a result of chronic thyroiditis. In the absence of these guideposts, differentiation between primary idiopathic thyroidal atrophy and atrophy secondary to failure of the anterior pituitary gland to produce thyrotropin is a laboratory exercise.

Patients who have hypothyroidism of the permanent variety without myxedema and patients who are "goitrous cretins" have goiter or at least some functioning thyroid tissue, and the presence of a thyroid may be apparent clinically. But the presence of tissue of less than goiter proportions may have to be evaluated in the laboratory. Also the question of the degree of preservation of thyroid function in such patients is answerable only in the laboratory. Therefore an understanding of the laboratory tests now available is essential.

B.M.R.—The maze of laboratory procedures which the modern clinician encounters in the evaluation of thyroid function is dense and constantly growing. Perhaps fewer errors in interpretation will accumulate if the first procedure ordered in any attempt to substantiate or refute a diagnosis of hypothyroidism is determination of the basal metabolic rate. All errors involved in this determination tend to make the answer too high. A low answer is quite meaningful. While the result of this test will certainly help to differentiate myxedema from hypothyroidism without myxedema and from euthyroidism, by being lowest in the first-named instance, it will not differentiate between the primary and secondary types of myxedema. Unfortunately one occasionally sees patients who seem to be healthy by all the usual parameters but whose basal metabolic rates are in the myxedematous range. Likewise there are occasional myxedematous subjects whose rates are in the range of hypothyroidism without myxedema. Because of these problems, the basal metabolic rate has fallen unjustifiably into disrepute within the past decade.

It takes about one and one-half hours to prepare and test a patient. The determination requires a tactful, interested technician of mature personality. There is no way to mass-produce this test, and, unfortunately, the machinery for the most accurate determinations is not the most attractive; it is an awkward-looking device known as a spirometer. Yet the performance of the test is a relatively simple matter, and technical errors are spotted readily. According to medical folklore, the shortcomings of the procedure are inherent in it. This may be true for hyperthyroidism, but in the diagnosis of hypothyroidism the errors lie in the way the test is conducted and are not theoretical limitations. Actually, few other diseases produce significant hypometabolism except through hypothyroidism.

PBI—A second helpful test is determination of the serum protein-bound iodine concentration. In principle the results of this test are more closely related to thyroid function than are the results of any other test. However, technically the procedure is difficult, and it can be performed only by a qualified chemist under the close supervision of a clinician. Relatively few clinicians have accurate PBI determinations available to them.

I^{131} tracer test—The last important test con-

cerned with the diagnosis of hypofunction of the thyroid is some form of the radioiodine tracer test. This involves the administration of an oral tracer dose of I^{131}. Heralded as the answer to the clinician's prayer in the diagnosis of thyroid disease, the tracer test with all its variations has been a mixed blessing. The results of measurements of radioactivity in the thyroid, urine or blood following administration of a tracer dose of I^{131} are at best only indirectly correlated with the clinical status of the thyroid gland. Many chemicals alter the distribution of labeled iodine in the body, usually in a way which lowers the uptake by the thyroid gland itself and results in simulating signs of hypothyroidism. Consequently the results of a tracer test, interpreted out of context, can be extremely misleading. In addition, the I^{131} tracer test entails problems if it is used in the evaluation of subjects who are being or have been treated for hyperthyroidism by any of the current methods. In these patients the handling of iodine by the thyroid is no longer related to their clinical status. Particularly vexing is the interpretation of a markedly depressed 24 or 48 hour radioiodine uptake in a radioiodine-treated, previously hyperthyroid patient who appears euthyroid clinically. Still, the results of the radioiodine uptake test in such patients need not lead to an incorrect diagnosis if one remembers that the uptake of radioiodine does not measure over-all thyroid function but merely one parameter of it. Subject to the same errors is an extension of the iodine uptake test, the conversion ratio. This is an additional measurement, often made at the same point in time as the uptake, of that fraction of the total amount of radioiodine in the blood which already has been metabolized by the thyroid and incorporated into some "hormonal" or "hormonelike" compound(s) which are protein-precipitable, butanol-extractable or ion-exchangeable.

Patients in the first clinical group of the classification presented previously (myxedema) should have negligible values for all these measurements, but euthyroid or even hyperthyroid patients can demonstrate the same results if a "chemical block" of some type is present. The problems are even greater in terms of interpretation of these tests in the second and third clinical groups (permanent hypothyroidism without myxedema, and cretinism), because these patients may have tissue that functions more or less as thyroid tissue; the I^{131} uptake and conversion ratio may range from zero to 100 per cent.

While all these procedures are used in the evaluation of thyroid function, no combination of those discussed so far is helpful in the differentiation of primary from secondary (or pituitary) hypothyroidism. The tests usually employed in the evaluation of anterior pituitary function may be helpful in this regard, especially if some yield normal results. However, any of these tests, or on occasion all of them, can yield abnormal results in primary hypothyroidism. Fortunately a more specific test of functional reserve of the thyroid gland has been developed. In its simplest form it is a comparison of the uptake of I^{131} by the thyroid gland before and after administration of exogenous thyrotropin. This test for thyroid integrity in patients with proved hypothyroidism is probably the best one available for this etiologic differentiation.

There are many other tests which are helpful in ruling out or establishing a diagnosis of hypothyroidism, including the serum cholesterol content, the electrocardiogram, and the serum protein fractionation. Yet, by and large these tests only call attention to the possibility of hypothyroidism and are too nonspecific to be of real diagnostic help.

Features of Hypothyroidism

Three features of hypothyroidism deserve special attention because they may overshadow the rest of the clinical picture and are useful points to remember for the recognition of otherwise atypical cases. These features are abnormal menstruation, psychosis and anemia.

The menstrual disorder can vary, but it follows a logical pattern. Apparently the basic abnormality is the failure of the hypothyroid patient to produce gonadotropins normally. The first evidence is inadequate ovulation. This may be manifested initially by infertility with normal menses or by cyclic but excessive

menstruation. In time the cycle becomes irregular and the type of flow varies unpredictably from spotting to hemorrhage. Finally the irregular cycle gives way to amenorrhea. Probably this latter eventuality heralds the loss of follicular stimulation and growth, and the endometrium at this point is inactive or even atrophic.

The psychosis is not too distinctive, but tends to resemble a depression. Actually some hypothyroid patients are merely withdrawn and are erroneously called psychotic, but many are diagnosed as being psychotic as a result of organic brain disease.

The anemia is "typically" a macrocytic one, but the "typical" anemia is seldom seen. The usual findings are microcytosis and hypochromia if menorrhagia is present, or normocytosis and normochromia if there are no bleeding problems.

It is interesting that these features of hypothyroidism, when present, often are controlled by suboptimal doses of desiccated thyroid and disappear before the patient is otherwise euthyroid. Consequently it is extremely important to decide whether or not a given menorrhagic, infertile, amenorrheic, psychotic or anemic patient is hypothyroid before using desiccated thyroid empirically. Otherwise, the treatment given may be wholly inadequate to control the basic problem; for instance, a dosage of 65 mg. of thyroid daily may control the menstrual difficulties but still allow the patient to remain symptomatically hypothyroid.

Therapy

The therapy of any of these syndromes of hypothyroidism is basically resolved into a program of replacement with desiccated thyroid substance. This is done best with the usual "crude" preparations of thyroid obtained from beef, sheep or hog glands. There is no need, by and large, for "purer" forms of the thyroid hormone(s), or for those forms that produce a metabolic effect faster.

One should always explain to the patient that such replacement therapy requires continual daily rations, "until death do us part." It is probably wise also to explain that there is a reasonable lag phase for the action of the medication. It takes 10 to 20 days for noticeable effects to be produced at the outset, and it takes a similar period for the effects of withdrawal of therapy to become evident.

Proper maintenance dosage varies with age and depends on the presence or absence of other health problems. When the best maintenance dosage has been established, it should be continued, since the patient will not accumulate the drug or become tolerant to it or overly sensitive to it. To maintain a euthyroid state, most adults with hypothyroidism require a dosage ranging from 130 to 190 mg. of desiccated thyroid daily.

It should be remembered that the true cretin is seldom rendered normal by any therapy. This realization may help the physician avoid the use of excessive replacement therapy, and the resulting unnecessary toxicity. It also may avoid raising the hopes of distraught parents unduly. It should never, however, interfere with the physician's attempt to achieve maximal benefit for the patient.

In general, patients with hypothyroidism are very grateful patients when treated correctly. It therefore behooves all of us to recognize the disease and treat it. This does not mean that all sick patients are hypothyroid or will benefit from desiccated thyroid; rather, the diagnosis must be made with care and deliberation.

Thyroxin Analogs and Their Place in Therapy

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Recent discovery of several naturally occurring thyroxin analogs has led to the study of a number of synthetic compounds having thyromimetic activity. The place of these thyroxin analogs in therapy is described in relation to replacement therapy for hypothyroidism (use of L*-triiodothyronine compared with desiccated thyroid and* L*-thyroxin) and to treatment of hypercholesteremia (experimental results with* D*-thyroxin,* D*-triiodothyronine, tetraiodothyroacetic and triiodothyroacetic acid, triiodothyropropionic acid, diiodothyroacetic acid and diiodothyroformic acid).*

EDWIN C. ALBRIGHT

THYROXIN analogs have been of interest to physicians and physiologists for many years. With the isolation of thyroxin by Kendall in 1915 and its synthesis by Harington in 1927, it became possible to study the metabolism of this hormone in man and experimental animals. From these fundamental studies has come an increasing understanding of pituitary-thyroid relationships, of steps involved in the biosynthesis of hormone within the thyroid gland and its transport in the circulation, and of the metabolism of the hormone in various body tissues. It has been recognized that while thyroxin is the principal thyroid hormone found in the gland and circulation, one active analog, L-3,5,3′-triiodothyronine, is also present in the gland, circulation and tissues.

More recently the acetic acid analogs of thyroxin and triiodothyronine have been found in tissue preparations as the metabolic products of these two hormones.[1] Considerable interest in these analogs has developed because of the possibility that one or both might be the form in which thyroid hormone acts in the tissues. Investigations of thyroid hormone metabolism have thus resulted in the discovery of several naturally occurring

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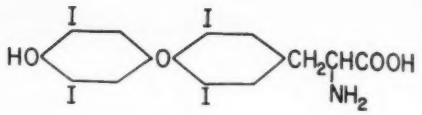
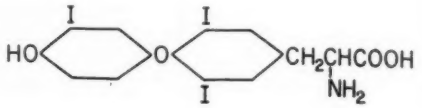
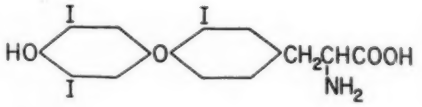
Thyroxin (3, 5, 3′, 5′-tetraiodothyronine)
L or D form



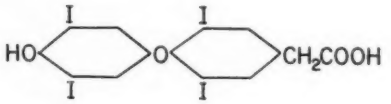
3, 5, 3′-Triiodothyronine
L or D form



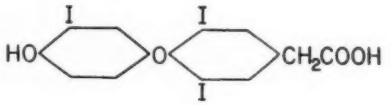
3, 3′, 5′-Triiodothyronine



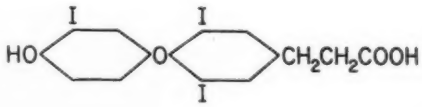
3, 5, 3′, 5′-Tetraiodothyroacetic acid



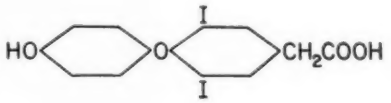
3, 5, 3′-Triiodothyroacetic acid



3, 5, 3′-Triiodothyropropionic acid



3, 5-Diiodothyroacetic acid



3, 5-Diiodothyroformic acid

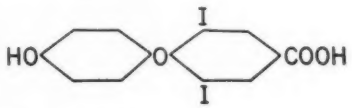


FIGURE 1. Chemical formulas of thyroxin and the various analogs referred to in the text.

analogs of thyroxin which are of physiologic and pharmacologic importance (figure 1).

At the same time, certain synthetic analogs of thyroxin have been studied in the hope of finding a compound that would decrease the metabolic rate, either by its action as a thyroxin antagonist or by inhibiting the pituitary and thereby leading to a decrease in thyroxin secretion. While thyroxin antagonists have been examined in experimental animals and man, none are of established clinical value at the present time. Compounds which inhibit the pituitary and secondarily curtail thyroxin secretion have in general been found to possess some calorigenic activity which has placed limitations on their clinical usefulness.

The foregoing remarks are not meant to imply that some dissociation of thyroid hormonal effects by structural alteration of the thyroxin molecule cannot be achieved. Great impetus was given to investigation of this possibility following the discovery of tetraiodothyroacetic acid and triiodothyroacetic acid,

acetic acid analogs of thyroxin and triiodothyronine, respectively. Lerman and Pitt-Rivers[2] reported that the administration of triiodothyroacetic acid to two myxedematous patients caused a fall in serum cholesterol and improvement of signs and symptoms without causing appreciable sustained rise in basal metabolism. This apparent dissociation of hormonal effects has been extensively studied using a number of thyroxin analogs.

Rawson and co-workers[3] recently reported observations on relative physiologic effects of several thyroxin analogs on a number of parameters of thyroid hormonal function, including uptake of I^{131}, goiter prevention, basal metabolic rate, inhibition of pituitary TSH-secreting tumors, and tadpole metamorphosis. Varying physiologic effects were obtained depending on the chemical structure of the analog tested. For example, L-3,5,3′-triiodothyronine was more active than thyroxin in most assays, while DL-3,3′-5′-triiodothyronine was much less active in all assays except for its relatively good ability to suppress I^{131} uptake by the thyroid. In tadpole metamorphosis, 3,5,3′-5′-tetraiodothyroacetic acid and 3,5,3′-triiodothyroacetic acid were 10 to 24 times as active as thyroxin, but one-tenth to one-fifth as calorigenic. Other analogs, such as 3,5,3′-triiodothyropropionic acid, were exceptionally active in stimulating tadpole metamorphosis yet possessed little effect on the basal metabolic rate. The same analog has been found to possess some ability to lower serum cholesterol without significantly elevating oxygen consumption. Thus, it is to be hoped that continuing study of thyroxin analogs will reveal compounds having certain selective pharmacologic properties without the complete physiologic effects of the thyroid hormone.

The place of thyroxin analogs in current therapy can be described best by considering first the problem of replacement therapy and second their possible role in treatment of hypercholesteremia.

Replacement Therapy

The problem of replacement therapy may be simplified by comparing the use of the major analog, L-3,5,3′-triiodothyronine, with older and more familiar preparations, desiccated thyroid and L-thyroxin.

Desiccated thyroid—In the vast majority of patients needing thyroid replacement therapy, desiccated thyroid U.S.P. provides very satisfactory results. It is readily available, reasonably uniform in potency, effective and inexpensive. The latter is an important consideration when medication has to be continued for many years. Attainment of maximal therapeutic effect is slow, requiring approximately seven days, and on withdrawal the basal metabolic rate falls gradually over several weeks to the pretreatment level. Thus, a very smooth, steady metabolic effect that is advantageous can be achieved with desiccated thyroid.

The usual dosage required to maintain an athyreotic adult in a state of euthyroidism is from 2 to 3 gr. (120 to 180 mg.) daily. Therapy in a myxedematous patient must be initiated cautiously, especially in the older patient, to avoid precipitation of myocardial ischemia. For this purpose, treatment should be started with ¼ gr. (15 mg.) daily for 7 to 10 days, after which the dosage is increased to ½ gr. (30 mg.) for another 10 days; additional increments of ½ gr. are made at intervals of 10 days to two weeks until a maintenance dosage level is reached. As a general rule, the older the patient and the longer the duration of myxedema, the more cautious the therapy should be. Development of anginal pain is a danger signal indicating that the older patient's tolerance for thyroid has been exceeded.

L-*Thyroxin*—Occasionally the physician may prefer to use the sodium salt of L-thyroxin, although it offers no practical advantage over desiccated thyroid for routine use, and no qualitative effect not obtained with desiccated thyroid. The rate of response is no different, and it is somewhat more expensive than desiccated thyroid. The usual dose of thyroxin needed to maintain euthyroidism is in the range of 0.1 to 0.2 mg. daily.

L-*3,5,3′-Triiodothyronine*—This naturally occurring analog of L-thyroxin exhibits a complete thyroid hormonal effect when adminis-

tered to athyreotic subjects. For this reason it is the one analog suitable for thyroid replacement therapy. Moreover, it possesses important properties which significantly modify its clinical effect as compared with either thyroxin or desiccated thyroid. Experimental evidence indicates that it is not firmly bound to serum globulin and is not well retained within the intravascular compartment, in contrast to thyroxin. It rapidly enters the tissues in relatively high concentration and exerts its metabolic effect. It is therefore not surprising that the significant difference between thyroxin and triiodothyronine lies in the speed of metabolic response. With triiodothyronine, a clinical effect on basal metabolic rate is observed within four to six hours after administration, with a maximal response occurring in 48 hours. Further, following cessation of treatment with triiodothyronine, the basal metabolic rate returns to pretreatment levels in from seven to nine days. This time-response curve is sharply accelerated in contrast to that of thyroxin or desiccated thyroid.

Triiodothyronine is therefore the agent of choice when it is essential to obtain a therapeutic response rapidly or when a rapid abolition of metabolic effect is desired after withdrawal of the drug. This is necessary relatively rarely, e.g., in psychosis associated with myxedema; in severe heart failure with myxedema; in a diagnostic trial of thyroid replacement therapy; and for suppression of thyroid-stimulating hormone either intermittently in patients with thyroidal cancer being treated periodically with radioactive iodine or continuously in patients with lymphocytic thyroiditis or thyrotropic exophthalmos. While triiodothyronine is particularly useful in these specific situations, it offers no real advantage over desiccated thyroid in the long-term therapy of established hypothyroidism.

As with the other preparations, therapy of the hypothyroid patient with triiodothyronine should be started with small doses (0.01 to 0.025 mg.), increased gradually to the full maintenance level, which is in the range of 0.075 to 0.125 mg. daily. It should be noted that determinations of protein-bound iodine in the plasma are of no value in assessing effectiveness of therapy, since triiodothyronine is not bound by serum protein.

Diagnostically, triiodothyronine is useful in evaluating the significance of an elevated radioiodine uptake. One week of therapy with 0.075 mg. of triiodothyronine will, by pituitary inhibition, result in the normalization of a second radioiodine study in the euthyroid patient but will not lower the high uptake of the thyrotoxic patient.

The use of such a potent hormone as L-3,5,3′-triiodothyronine should be limited to (1) those patients in whom replacement therapy is necessary for well-documented thyroid deficiency and (2) those in whom it is desired to suppress pituitary-thyroid function for either diagnostic or therapeutic reasons. Indiscriminate use of this compound in the treatment of exogenous obesity, chronic fatigue states and hypometabolism is not recommended.

Thyroxin Analogs and Cholesterol Metabolism

It has long been known that replacement therapy with desiccated thyroid will lower the hypercholesteremia of hypothyroidism to normal values. There have been relatively few studies of its effect in euthyroid, normocholesteremic patients. Strisower and associates[4] reported that in euthyroid, schizophrenic patients with normal cholesterol values the administration of 195 mg. of desiccated thyroid daily for three weeks produced a fall in cholesterol from 216 to 157 mg. per cent. This fall was not maintained by this dosage level, however; 260 mg. daily was required for this purpose. These authors reported a concurrent fall in serum lipoprotein levels and atherogenic index in these patients. More recently, similar results were obtained with L-thyroxin used as a hypolipoproteinemic and hypocholesteremic agent.[5]

Thus, it appears likely that moderate reduction in serum cholesterol levels can be achieved with desiccated thyroid or L-thyroxin if the patient is able to tolerate some increase in oxygen consumption and cardiac irritability. Unfortunately the latter effect of thyroid hormone is apt to be the limiting factor in the

patient with heart disease who is hypercholesteremic and most in need of therapy. A wide variety of thyroxin analogs have been studied in regard to their ability to lower serum cholesterol without inducing an undesirable increase in oxygen consumption or cardiac irritability.

D-*Thyroxin*—This stereoisomer of the natural hormone has been reported to suppress production of thyroid-stimulating hormone by the pituitary and to modify serum cholesterol levels. In euthyroid subjects with intact thyroid glands, Starr[6] found that administration of D-thyroxin in doses in the range of 5 mg. daily resulted in a rise of serum cholesterol, due presumably to suppression of thyroid glandular activity via the pituitary. On the other hand, in the absence of the thyroid, Starr[7] found that 1 to 2 mg. of D-thyroxin given daily to myxedematous patients lowered serum cholesterol in three to four weeks without raising the basal metabolic rate or altering the electrocardiogram. Larger doses (10 mg.) of D-thyroxin were found in one myxedematous patient to be calorigenic and hypocholesteremic, although with this dosage level the possibility exists of contamination of the medication with as little as 1 per cent of L-thyroxin, which would provide an effective dose of the natural hormone. At present, the use of D-thyroxin to lower elevated serum cholesterol levels in euthyroid or myxedematous subjects must be considered experimental.

D-*3,5,3′-Triiodothyronine*—The stereoisomer of the naturally occurring L-3,5,3′-triiodothyronine has been studied in a small number of euthyroid, hypercholesteremic patients.[8] When administered in a dosage of 1 mg. daily for four weeks to four patients, a fall in cholesterol was observed ranging from 21 to 146 mg. per cent as compared with similar patients given placebos. Negligible effects on the basal metabolic rate and thyroid uptake of radioiodine were noted at the close of the treatment period. This analog appears to have promise in treating hypercholesteremia.

3,5,3′-Triiodothyroacetic acid and 3,5,3′-5′-tetraiodothyroacetic acid—Following the initial report on the hypocholesteremic effect of triiodothyroacetic acid in myxedema by Lerman and Pitt-Rivers,[2] a subsequent study[9] in myxedematous patients again demonstrated the effect on serum cholesterol of both acetic acid analogs and called attention to their calorigenic effect, which was quite definite although evanescent when compared with thyroxin. Subsequent papers by Trotter[10] and Goolden[11] confirmed the weakly calorigenic effect of these analogs and their ability to lower cholesterol moderately in both myxedematous and euthyroid subjects. Trotter[10] concluded that triiodothyroacetic acid was not likely to be particularly useful in lowering cholesterol levels of euthyroid persons. Oliver and Boyd[12] expressed similar conclusions. They found that 3 to 5 mg. of triiodothyroacetic acid daily did lower plasma cholesterol and cholesterol-phospholipid ratio and the B-lipoprotein-cholesterol ratio without raising the basal metabolic rate in euthyroid, hypercholesteremic men with coronary disease. Unfortunately, in two of the 12 patients angina of effort developed, even though the basal metabolic rate was not raised, and the fall in cholesterol could not be maintained for long even by raising the dosage of triiodothyroacetic acid. Oliver and Boyd concluded that triiodothyroacetic acid may not prove suitable for long-term treatment of hypercholesteremia in patients with clinical coronary disease.

3,5,3′-Triiodothyropropionic acid—The propionic acid analog of 3,5,3′-triiodothyronine has been administered to both euthyroid and hypothyroid patients by several groups of investigators. Sachs and Arons[13] reported that serum lipids were depressed by 1 to 6 mg. daily, the decreases ranging from 11 to 70 per cent in the hypothyroid group and 10 to 28 per cent in the euthyroid, normocholesteremic group. However, in two euthyroid patients who were followed for more than six months the lipid depression was not completely sustained. A definite calorigenic effect was noted in the hypothyroid group, while no consistent change in basal metabolic rate was seen in the euthyroid group.

Schaefer and Adlersberg[14] reported that triiodothyropropionic acid in an average dosage of 2.5 mg. daily given to 17 euthyroid patients lowered serum cholesterol from 269

to 234 mg. per cent (−13 per cent, range 0 to −23 per cent), and in hypercholesteremic patients it lowered the serum cholesterol from 353 to 289 mg. per cent (−18 per cent, range 0 to 44 per cent). In one patient, thyrotoxicity developed after four months, but in the others there was no evidence of significant calorigenic effect. Angina did not develop in any of the five patients with coronary disease.

Weston[15] noted an average fall in serum cholesterol of 22 per cent in 12 euthyroid patients on triiodothyropropionic acid (1 to 12 mg. per day). Although one patient exhibited nervousness and tremor with a dosage of 6 mg. per day, no weight loss, increase in basal metabolic rate, or cardiac symptoms were noted in the group.

Experimental studies in animals—Ruegamer and co-workers[16] have tested a number of thyroxin analogs for their relative effects on tissue cholesterol concentrations, oxygen consumption and growth in hypercholesteremic rats. Of 33 analogs tested, 3,5-diiodothyroacetic acid and 3,5-diiodothyroformic acid appeared to exert the greatest preferential effect on tissue cholesterol and lipid concentrations without affecting oxygen consumption and growth. As to the mechanism of action, dietary C^{14}-labeled cholesterol absorption was unaffected by feeding diiodothyroacetic acid. However, the analog greatly enhanced the rate at which cholesterol and lipid were mobilized from liver depots. These authors suggested that for the prevention and reversal of hypercholesteremia in the rat, a thyroxinlike molecule with a side chain of at least two carbons is needed, and that the phenol group is not important but at least one iodine in position 3 is required.

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The Diagnosis and Treatment of Toxic Nodular Goiter

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Because toxic nodular goiter occurs frequently in elderly persons who have associated degenerative diseases, it presents unusual problems in diagnosis and treatment. The difficulty in diagnosis may be compounded by the sporadic function of the toxic thyroid nodule with fluctuating clinical and laboratory findings.

The pathogenesis of toxic nodular goiter is reviewed, as are the clinical picture, laboratory findings, and choice of therapy. In general, surgical resection is the most effective definitive form of therapy, but it carries a significant risk which must be evaluated carefully.

HYPERTHYROIDISM is a symptom complex resulting from an excess of thyroid hormone in relation to the individual's requirements. An excess of thyroid hormone may be due to ingestion of thyroid substance (factitious hyperthyroidism), to a destructive process in the thyroid gland with liberation of stored hormone (subacute thyroiditis), to excessive production of hormone by one or more adenomas of a nodular goiter, or to diffuse hyperplasia of the thyroid (Graves' disease). Although hyperthyroidism is a syndrome of heterogeneous nature, it is often erroneously considered as a single disease entity.

This lack of distinction is particularly unfortunate as regards toxic diffuse goiter (Graves' disease or exophthalmic goiter) and toxic nodular goiter (toxic adenomatous goiter). Although these disorders have hyperthyroidism in common, they differ in pathogenesis, histologic appearance, clinical picture and therapeutic approach. The importance of making this distinction is apparent in considering therapy, since success or failure is often dependent on an understanding of the more basic physiologic changes accompanying the hyperthyroid state. It is the aim of this article to review the problem of toxic nodular goiter from a clinical viewpoint.

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Pathogenesis

Toxic nodular goiter generally has its origin in the simple diffuse colloid goiter which oc-

curs relatively early in life. Simple goiters have been observed most commonly in areas of iodine deficiency. Since the introduction of iodine into the diet in a variety of ways, the incidence of simple goiter has been reduced markedly. Consequently, a reduced incidence of nodular goiter may be expected in the future if it is not already apparent. It is evident that since the simple iodine-deficient goiter is a precursor of the multinodular goiter, the geographical distribution is similar. The incidence in coastal areas is low when compared with that in the Great Lakes region. Other factors than iodine deficiency are involved in the formation of simple goiter, however, and the associated nodular goiter is not confined to areas of iodine deficiency. Enzymatic defects in the synthesis of thyroid hormone, alterations in sex hormones during puberty and pregnancy, and goitrogen-containing diets may be implicated in some cases, while in others the cause remains obscure.

The pathologic changes leading to nodule formation in the simple colloid goiter are not clearly understood.[1-3] After some variable interval of time, the simple goiter undergoes "involution." During this stage, minute islands of cells make their appearance and assume functional hyperactivity. These islands may revert to their previous relatively inactive state, or they may enlarge and give rise to nodules which eventually attain macroscopic size. The variable histologic and physiologic status of these microscopic nodules in the involuting simple goiter may persist into the macroscopic nodular phase. A nodule may consist chiefly of colloid with relatively little cellular component, or it may be extremely cellular with little colloid. Some of the nodules have a thin capsule and the cellular pattern simulates that of an adenoma. Consequently, the multinodular goiter is also referred to as an adenomatous goiter. The true adenoma, however, generally arises as a solitary nodule in an otherwise normal gland and has a well-defined capsule.

The stimulus to nodule formation in a simple goiter is not known. Perhaps the intermittent excess of thyroid-stimulating hormone (TSH) from the pituitary, which is instrumental in the development of the simple goiter, also leads to involutional changes and nodule formation.

Since multinodular goiter usually arises from simple diffuse goiter, and since time is required for its development, it follows that the incidence of nodular goiter should be low in childhood but should increase with age. It is unusual to see a typical multinodular goiter before the age of 30 years. Simple goiter may not be uncommon in the second and third decades of life, and involutional changes may already be present; however, the nodules usually are not large enough to be detected by palpation. The increasing incidence of multinodular goiter with age is so striking that in some endemic goiter areas it would not be surprising to palpate a goiter in 25 per cent of persons over the age of 50 years. In the same area, the incidence of multinodular goiter as determined by routine postmortem studies might exceed 50 per cent, the difference being due to the small impalpable nodules found by the pathologist or to the lack of careful palpation of the neck by the clinician.

With this brief background regarding the development of the multinodular goiter, we may consider more specifically the *toxic* multinodular goiter. Throughout the period of development of the goiter, the thyroid remains generally responsive to normal regulating mechanisms which are largely mediated through the pituitary gland by TSH. At some time and for unknown reasons, one (or more) of the nodules begins to function independently. The nodule accumulates iodine and produces thyroid hormone regardless of the body's requirements. At this point, a "hot nodule" may be demonstrated by careful scanning of the thyroid after a test dose of radioiodine. The amount of thyroid hormone produced by the nodule depends on its functional capacity. This is determined by the degree of activity in the nodule, and also by its size. In its early stages of autonomous function, the "hot nodule" elaborates only small amounts of hormone representing a fraction of the amount required by the body. As the nodule increases in activity and size, it produces a greater pro-

portion of the body's requirement, and the normal regulating mechanisms of the body cause a proportional decrease in function of the rest of the thyroid gland. Eventually, the "hot nodule" produces all the hormone required, and the rest of the gland is relatively inactive. Up to this point, although a "hot nodule" has been present, thyroid hormone has not been produced in excess of the body's needs, and the patient has not been hyperthyroid. Eventually, the nodule's production of hormone exceeds the requirement of the body, and hyperthyroidism results. At this time the term toxic nodular goiter becomes appropriate.

This evolutionary picture of the toxic nodule has been depicted as a slowly progressive state of activity. More likely, activity is slowly progressive, but sporadic in nature. This implies that the nodule does not function at a constant rate; rather, from week to week, day to day or even hour to hour, the amount of thyroid hormone produced or released may vary. This concept of variability in state of function is not new when one considers other functioning endocrine tumors. The pheochromocytoma and the pancreatic islet-cell tumor are hormone-producing tumors whose clinical pictures reflect the sporadic nature of their function. This sporadic function of the "hot nodule" of the thyroid may partially account for the difficulty in diagnosis because of the variable clinical picture and the variable laboratory findings.

Clinical Picture

In reviewing the development of the toxic thyroid nodule, one may better understand the clinical picture as it is presented to the practicing physician. The patient often recalls having had a simple goiter in childhood or adolescence. He may recognize a persistence of the goiter, perhaps with the development of one or more large nodules. The goiter may attain a certain size and remain so for many years, or it may progressively increase in size. The toxic nodule is more likely to be found in women, as is its precursor the simple colloid goiter. The age group affected is more likely to be the 50 to 80 year group, in contrast to the 20 to 50 year group of hyperthyroid individuals with Graves' disease. The onset of hyperthyroidism tends to be insidious and relatively mild with toxic nodular goiter, while with Graves' disease the onset is usually abrupt and thyrotoxicosis is often severe.

Exophthalmos and related ophthalmopathy are never features of toxic nodular goiter. Minor eye signs, such as a stare, mild lid retraction and infrequent blinking, may be observed but cause no symptoms. The presence of exophthalmos in a hyperthyroid patient with a nodular goiter is indicative of Graves' disease, which may exist coincidentally with a multinodular goiter. In such circumstances, it is not a nodule which is overactive but rather the diffusely hyperplastic thyroid tissue in which nodules may be embedded. Scanning of the thyroid in conjunction with the radioiodine uptake test may be helpful in making this differentiation.

Hyperthyroidism due to toxic nodular goiter is often associated with degenerative disorders which frequently afflict persons in the older age groups. Under these circumstances, even mild hyperthyroidism may create unusually severe consequences. This is particularly true of the degenerative vascular diseases, the symptoms and findings of which may so dominate the clinical picture that the thyroid problem is overlooked. This situation has been called "masked" hyperthyroidism. Unfortunately, a compromised cardiovascular system is particularly vulnerable to the increased load imposed on it by even mild hyperthyroidism, and it is particularly important to recognize and treat the thyroid disease in addition to the underlying vascular disease.

Symptoms usually attributed to hyperthyroidism may be very mild or lacking in a patient with toxic nodular goiter. These include weight loss in spite of an excessive appetite, tendency to loose stools or diarrhea, decreased tolerance to heat, increased perspiration, nervousness and palpitation. We have been impressed with certain relatively minor findings in some patients with toxic nodular goiter. Hyperthyroidism is suggested in the elderly patient who is unusually alert and active, who has a "good" appetite, who lacks

the usual intolerance to cold, and who is *not* troubled with constipation. In the absence of complicating illnesses, these aspects of hyperthyroidism appear to be more beneficial than detrimental.

The development of hyperthyroidism due to a toxic nodule is suggested by a decrease in the size of a nodular goiter which has been present for many years. This is due to the atrophy of the remaining portions of the gland when the "hot nodule" produces excessive amounts of hormone.

Diagnosis

Hyperthyroidism should be considered in any patient with a goiter, particularly in the middle or older age groups when the presenting problem is one of cardiovascular disease. The diagnosis should be entertained in such patients when they respond poorly to the usual cardiac management, even when a goiter is not palpated. A goiter may be discovered within the thoracic cage by chest roentgenograms or by scanning after a tracer dose of radioiodine. Fortunately, most of these substernal or intrathoracic nodular goiters have upward extensions which can be detected by careful palpation of the suprasternal area while the patient swallows or coughs.

A high index of suspicion is not enough to make a diagnosis. Symptoms and physical findings may be so minimal or obscured by associated disorders as to be inconclusive. The complaints of "nervousness," decreased heat tolerance, increased sweating, palpitation, weight loss and the associated physical findings are by no means specific for hyperthyroidism. The clinician often must turn to the laboratory for help in diagnosis.

Laboratory Findings

The laboratory tests of thyroid function often assume considerable importance in establishing the diagnosis of toxic nodular goiter. The vagaries of the toxic nodule, however, impose serious limitations on these laboratory tests.

Basal metabolic rate—The basal metabolic rate (B.M.R.) may be helpful; however, conditions other than rate of thyroid function affect this measurement. Cardiac failure, anemia, malignancies and respiratory diseases may increase the basal metabolic rate markedly. The frequent occurrence of these disorders in patients in whom the presence of toxic nodular goiter is suspected decidedly limits the value of the B.M.R. as a diagnostic tool. Lack of cooperation by the elderly patient may also limit the usefulness of the test. In the absence of such complicating factors, it is still a valuable adjunct in diagnosis and in following the patient's course during therapy. Also, a normal basal metabolic rate tends to rule out hyperthyroidism.

Serum cholesterol—The level of cholesterol in the serum is of almost no diagnostic value in toxic nodular goiter. The level tends to decrease with more severe hyperthyroidism, but levels distinctly below the wide normal range are seldom observed.

Serum protein-bound iodine—The PBI level, being a direct measure of the circulating thyroid hormone, is more valuable than the basal metabolic rate or the serum cholesterol level, especially in the elderly patient. Generally, the degree of hyperthyroidism as observed clinically correlates well with the level of the PBI. With toxic nodular goiter, this value is usually in the range of 7 to 12 μg. per 100 cc. of serum. The marked elevations (15 to 25 μg.) often seen with Graves' disease are only rarely observed with toxic nodular goiter. In an earlier study,[4] we observed that in 15 of 23 patients in whom the presence of toxic nodular goiter was ultimately proved, only minimal elevations of PBI were seen, i.e., values between 7.0 and 9.0 μg. per 100 ml. (normal range 3.5 to 7.0 μg.) at the time of initial observation. Thus, even slight elevations must not be ignored.

Since the functional status of the toxic nodule may vary from day to day, and the amount of thyroid hormone released may vary, the serum PBI level may also vary. We have observed this variability in some patients with toxic nodular goiter. The PBI may vary between high normal and hyperthyroid ranges from day to day or week to week. Such fluctuations in the PBI are not observed in normal individuals; rather, the level is remarkably con-

stant. A patient who presents evidence of paroxysmal cardiac arrhythmia may have a normal PBI on one occasion and a high PBI on another. Such cardiac arrhythmias may be precipitated by sudden excesses of circulating thyroid hormone, particularly when there is some underlying cardiac disease. In patients with nodular goiters the presence of atrial fibrillation rather than a sinus rhythm greatly increases the probability of hyperthyroidism.[5] Under these circumstances, if the clinical picture suggests toxic nodular goiter, the finding of a normal PBI level on one occasion is not conclusive evidence against that diagnosis. Repeated PBI determinations may demonstrate the fluctuations which reflect sporadic thyroidal hyperactivity.

The frequent association of nodular goiter and cardiac failure presents another problem in using the PBI level as a diagnostic aid. Patients who have received mercurial diuretics will have falsely low PBI values for 24 or even 48 hours after the medication has been administered. This depression may be so marked that a hyperthyroid patient may have a PBI level in the hypothyroid range. This spurious depression of the protein-bound iodine occurs when the digestion-distillation method is used, because the mercury interferes with the chemical determination.

The value of the serum PBI determination is also limited by the presence of a wide variety of iodine-containing compounds. The problem of inorganic iodides such as potassium iodide, which is frequently used as an expectorant, can be overcome by determination of the butanol-extractable iodine (BEI). By this method, inorganic iodides are removed before the final measurement of hormonal iodine. Unfortunately, organic compounds containing iodine, such as the contrast media used in radiologic procedures, cannot be excluded by this technic. Contrast materials used for urographic procedures persist for as long as three months, those used for cholecystography persist for as long as six months, and those used for bronchography and myelography persist indefinitely.

In spite of its shortcomings, the serum PBI determination is probably the most valuable aid in diagnosis of hyperthyroidism due to toxic nodular goiter.

Radioiodine uptake—Studies to determine thyroidal uptake of radioiodine have become widely available within recent years and have proved of value in diagnosis. The over-all uptake is rarely in the high ranges commonly seen with the diffuse toxic goiter of Graves' disease. Rather, moderate or minimal elevations of total uptake are found with toxic nodules, and frequently the values are well within the normal range.[6]

A very valuable aspect of the uptake study is the scan of the thyroid. This can be performed manually using a collimated probe detector, or a more elaborate automatic scanning device may be employed. In either case, it is usually not difficult to detect even a small nodule containing a high concentration of radioiodine. The finding of one or more of these "hot nodules" has obvious significance. It is even more significant when the remaining portions of the thyroid have relatively low concentrations of iodine, since this indicates that the nodules are independently hyperfunctioning.

The finding of a "hot nodule" and an elevated total I^{131} uptake provides strong evidence for toxic nodular goiter. The finding of a "hot nodule" with a normal total I^{131} uptake provides presumptive evidence of a toxic nodular goiter, and in view of the clinical picture may be sufficient for diagnosis and subsequent therapy. Naturally, PBI determinations and an accurately performed B.M.R. also add precision to the diagnosis.

A number of ancillary procedures employing radioactive materials have been used in an attempt to define the diagnosis more clearly in doubtful cases. These include the conversion ratio, PBI^{131}, and studies of the uptake of triiodothyronine-I^{131} from the patient's serum by red blood cells or resins. At present, none of these procedures has proved to be of any great value in the diagnosis of toxic nodular goiter.

The radioiodine uptake test may be invalidated by many medications and by certain materials employed diagnostically, particularly those which contain iodine. These result in

spuriously low values. Since these same materials cause falsely elevated PBI values, these two most valuable tests of thyroid function may be rendered of little value.

When the laboratory tests are inconclusive in establishing a diagnosis of hyperthyroidism, a thyroid suppression test may be performed. The administration of triiodothyronine in a dose of 100 μg. daily for seven days to normal subjects causes a decrease in radioiodine uptake to below 50 per cent of the initial value. In patients with toxic goiters, little or no depression of the uptake will be noted.[7]

Each of the tests commonly in use measures a different aspect of thyroid function. Consequently, these tests provide complementary information. In many instances several or all of the available tests may be desirable to define the difficult diagnostic problem.

Under circumstances where the clinical features and all available laboratory studies fail to differentiate the euthyroid from the hyperthyroid state, a therapeutic trial may be indicated. An adequate trial with antithyroid drugs may be carried out over a two or three month period. The results of treatment even in cases of borderline hyperthyroidism may be dramatic and conclusive. A negative or questionable result after an adequate trial would indicate that therapy should be discontinued, but prolonged observation may be desirable with a re-evaluation at a later time.

Therapy

Although generalizations can be made regarding therapy of toxic nodular goiter, each patient presents a different problem and therapy must be individualized.

Surgical treatment—In general, surgical resection of the goiter is the most effective definitive form of therapy. In a single maneuver, the toxic nodule as well as most of the other thyroid nodules can be permanently removed. This eliminates the immediate source of difficulty as well as potentially toxic nodules. Removal of a large goiter is not only cosmetically desirable but is often necessary for the relief of pressure symptoms. The intrathoracic goiter likewise is best managed surgically. Another indication for surgical excision is suspicion of malignancy. Although carcinoma is rarely encountered in a toxic nodular goiter, the desirability of a histologic diagnosis becomes apparent when the goiter is unusually hard or fixed or increasing in size.

Unfortunately, surgery cannot be performed without significant operative and postoperative risk, particularly in elderly patients with cardiovascular disease. The advantages of surgery must be carefully weighed against its disadvantages before a decision is made. Undue risk should be avoided.

When surgery is contemplated, the need for preoperative therapy must be considered. In a patient with mild hyperthyroidism and without cardiovascular complications, a 10 to 14 day course of Lugol's solution may be sufficient preparation. When hyperthyroidism is more marked or when cardiac disease coexists, a euthyroid state should be attained before operation. This is best accomplished with antithyroid medication for six to eight weeks, adding Lugol's solution during the 10 days preceding operation. Details of medical therapy are discussed later.

"Thyroid storm" is a rare complication of surgery for toxic nodular goiter, particularly with adequate preoperative preparation.

Postoperative follow-up should not end with the healing of the incision. Although most surgical complications occur at or near the time of surgery, hypothyroidism may not become manifest for several months.

Radioiodine—Therapy with radioiodine is usually effective in treating toxic nodular goiter. However, results are not as immediately predictable as are those of surgical therapy. Relatively large doses of I^{131} (5 to 25 mc or even more) are frequently needed to establish a euthyroid state, because of the low and perhaps inconstant uptake of iodine by the toxic nodule. Calculation of dosage for the individual patient is difficult, if not impossible, and empiric dosage schedules are often used. Two or more therapeutic doses may be required at two to three month intervals. Fortunately, since the more normal tissue surrounding the "hot nodule" is physiologically inactive, it accumulates little radioiodine and

little radiation damage occurs. Consequently, there is a low incidence of permanent myxedema in these patients even when large doses of radioiodine are used.

The advantages of radioiodine therapy over surgery are related to the operative and postoperative complications, including risks of anesthesia, excessive bleeding, tracheal collapse, recurrent laryngeal nerve damage, hypoparathyroidism and wound infection. None of these problems arises with radiation therapy. Exacerbation of the hyperthyroid state by release of hormone within the 10 days following administration of the therapeutic dose is a decidedly unusual occurrence, although this problem arises occasionally with therapy of diffuse toxic goiter. In patients with serious pressure symptoms related to nodular goiter, the radiation inflammation may cause serious obstructive problems. In such patients, radioiodine should be given only after special consideration.

In certain patients who have severe symptoms because of hyperthyroidism, it may be advisable to institute therapy with antithyroid medication (e.g., propylthiouracil) one or two days after the administration of the therapeutic dose of I^{131}. With this additional drug therapy, the patient's condition should improve more rapidly than might be expected from radioiodine therapy alone. After two or three months, the antithyroid drug is discontinued to determine whether the therapeutic dose of radioiodine was sufficient or whether another dose should be given.

The theoretical limitations to therapy with radioiodine (subsequent malignancy or genetic mutations) are seldom serious considerations when dealing with toxic nodular goiter. Most patients are beyond the age of 40 years, and the possibility of inducing carcinoma, leukemia or genetic aberrations in this age group appears to be extremely remote.

As is true following surgery, the patient treated with radioiodine should be observed closely for several months to evaluate the clinical response. If indicated by a persistence of hyperthyroidism, subsequent therapeutic doses may be given at two to three month intervals.

Medical management—Certain persons are poor candidates for surgery because of cardiovascular or other complications. They may also be poor candidates for radiation therapy because of pressure manifestations or very low uptake of radioiodine. Others may refuse these more definitive forms of therapy. Under these circumstances, medical management must be employed. This implies long-term therapy with an antithyroid drug. The choice of antithyroid drug is an individual one and depends on the experience and preference of the physician. The thiouracil derivatives are the most widely used. Recently, there has been a renewed interest in the therapeutic application of some of the agents which block iodine trapping, such as potassium perchlorate. The efficacy of these agents in the prolonged therapy of hyperthyroidism remains to be evaluated. Iodine solutions (e.g., Lugol's solution) produce unimpressive results, particularly when used over prolonged periods, and generally have no place in long-term therapy of hyperthyroidism. Because of its relative safety at therapeutic dosage levels, we have used propylthiouracil in preference to other drugs.

When using propylthiouracil, one must bear in mind that although it may block thyroid hormone synthesis immediately, this effect diminishes markedly within a few hours. To maintain an adequate block, doses should be given at six hour intervals. The initial dosage level should be about 600 mg. daily. If a satisfactory therapeutic response is not observed within three weeks, the daily dosage may be increased to 800 or even 1000 mg.

When a euthyroid state has been achieved, as determined by clinical or laboratory evaluation, the dosage may be reduced to the amount necessary to maintain adequate control. This amount varies among patients and also in the same person from month to month. Consequently, titrating the dosage presents a definite problem involving frequent careful evaluation of the patient's status and readjustment of dosage. With inadequate therapy, the patient may rapidly resume his hyperthyroid state; with excessive therapy, he may become hypothyroid. This latter state may present a serious problem if it persists long

enough to result in excessive production of TSH by the pituitary gland. This, in turn, causes hyperplasia of the thyroid with an increase in size of the goiter. When this occurs in an already large goiter with compression symptoms, serious consequences may result.

A very effective way of by-passing this problem of titrating dosage levels of antithyroid drugs is to add thyroid substance to the therapeutic regimen after the initial period of therapy. Maintenance with 2 or 3 gr. of desiccated thyroid plus 200 to 450 mg. of propylthiouracil daily may be continued indefinitely without the danger of increasing the size of the goiter. Actually, a decrease in size may be anticipated.

When prolonged antithyroid therapy is employed it should probably be continued for at least a year. At the end of that time, the antithyroid drug may be discontinued abruptly and the dosage of desiccated thyroid decreased progressively and finally discontinued over a period of several months. This slow withdrawal allows for gradual re-establishment of normal pituitary-thyroid relationships and avoids sudden marked stimulation of the thyroid. Unfortunately, many patients with toxic nodular goiter will have a recurrence of hyperthyroidism and therapy must again be initiated. Because of this high recurrence rate, most patients who are treated medically are resigned to lifelong drug therapy. This is important to realize before therapy is begun, since success depends on the patient's cooperation and his acceptance of the expense.

If, during the course of therapy with antithyroid medication, the status of the patient improves to the extent that he becomes a good surgical candidate, surgery may be undertaken as an elective procedure. If, on the other hand, a decision is made to treat the patient with radioiodine, both antithyroid drug and desiccated thyroid must be discontinued before a therapeutic dose of radioiodine can be given. For a reasonable re-evaluation of the level of thyroid function, antithyroid medication should be withdrawn for at least two weeks and desiccated thyroid should be discontinued at least four weeks before iodine uptake studies are done and a therapeutic dose is administered.

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Primary Hyperparathyroidism

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Diagnosis of primary hyperparathyroidism is still based on indirect procedures which detect the biochemical disturbance caused by excessive excretion of parathyroid hormone, but an encouraging start has been made toward direct measurement of hormone concentration in tissue fluid. Only a constant awareness of the varying manifestations of the disease can result in recognition of more cases during life.

Some of the aspects of primary hyperparathyroidism discussed are clinical manifestations, biochemical disturbances, radiologic and histologic features, and differential diagnosis.

PRIMARY hyperparathyroidism is a state of uncontrolled overproduction of parathyroid hormone. The resulting biochemical disorder leads to skeletal, renal and systemic problems.

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Actions of Parathyroid Hormone

Parathyroid hormone regulates the physicochemical equilibrium between tissue fluid and skeletal mineral. In the normal state, parathyroid hormone and vitamin D together maintain the ionic calcium of the extracellular fluids at a concentration of about 6 mg. per cent, any variation being corrected by a compensatory reduction or increase in parathyroid secretion. The intimate mechanism whereby the hormone regulates the calcium concentration is not fully understood but may be connected with the concentration of hydrogen ion in the vicinity of the bone cell.[1]

Parathyroid hormone also exerts a phosphaturic action on the kidney which tends to lower the serum phosphate and to raise the phosphate clearance. It is generally believed that this effect is due to inhibition of phosphate reabsorption in the proximal tubule, but it has been suggested recently that it may be due to phosphate excretion by the distal tubule.[2]

Other actions of parathyroid hormone on the kidney are less well known but may be of no less clinical significance. Intravenous injection of parathyroid extract is followed by an increase in the excretion of sodium, potassium, chloride and bicarbonate,[3] and repeated injections lead to a reduction in water re-

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TABLE 1

SERUM CALCIUM CONCENTRATION IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM WITH AND WITHOUT BONE DISEASE*

SERUM CALCIUM CONCENTRATION (MILLIGRAMS PER 100 ML.)			
With bone disease		*Without bone disease*	
16.1	14.1	13.0	13.1
13.2	17.6	12.3	15.4
16.1	13.7	10.9	12.7
16.4	14.3	13.2	11.2
13.2	18.7	16.3	14.5
20.6	13.2	13.1	11.6
14.6	12.6	13.3	12.5
18.7	15.5	10.4	14.0
13.6	11.8		12.2
16.8	MEAN: 15.3		MEAN: 12.9

*From data of Glenn.[12]

absorptive capacity.[4] There is also some evidence that the hormone reduces calcium clearance.[5] It has been suggested that the hormone promotes calcium absorption[6] but this is more probably a manifestation of adaptation to negative calcium balance.[7]

Clinical Manifestations of Parathyroid Overactivity

Parathyroid tumors can occur at all ages. In the largest recent series[8] there were 117 women and 90 men. This sex ratio probably is more accurate than the larger preponderance of women which was noted in earlier series.

The clinical manifestations of primary hyperparathyroidism are so diverse as almost to defy classification. The majority of cases are discovered in the investigation of renal calculous disease, particularly bilateral recurrent calculi and nephrocalcinosis, but Albright's suggestion that 5 per cent of cases of urinary calculus would prove to be primary hyperparathyroidism[6] has not been borne out by recent experience of most workers. Striking exceptions are provided, however, by the reports of Chambers and associates[9] and McGeown and Morrison.[10]

Stone formation and renal calcification in primary hyperparathyroidism are not due solely to hypercalcinuria. Equivalent degrees of hypercalcinuria may be seen in other conditions, such as hyperthyroidism, without stone formation. An important contributing factor may be reduced excretion of hydrogen ion; this is known to follow injection of parathyroid extract[3] and has been noted recently in several clinical cases.[11] In certain respects, therefore, primary hyperparathyroidism resembles renal tubular acidosis.

The elevated serum calcium which is a cardinal feature of primary hyperparathyroidism usually leads to hypercalcinuria. Unless the intake of calcium is very high, this must involve the continuous removal of mineral from the skeleton. In most cases the resulting bone lesion is simple osteoporosis, but in some instances classic osteitis fibrosa develops. Many patients complain of bone pains, and particularly of backache, and some present with fractures. It seems that the incidence and perhaps the severity of the bone disease in hyperparathyroidism are related to the serum calcium concentration[12] (table 1), perhaps because in the presence of normal renal function serum calcium governs urine calcium and urine calcium determines the severity of negative calcium balance.

Hypercalcemia is also responsible for the nausea and vomiting which are not uncommon presenting symptoms when the calcium concentration exceeds about 15 mg. per cent, and it may also account for the hypotonia which is another clinical feature.

Polyuria and polydipsia have frequently been attributed to hypercalcemia in the past but are more probably due to the impairment of renal concentrating power mentioned previously.[13]

Other clinical features are less easy to explain. Pancreatitis has been reported in association with primary hyperparathyroidism both preoperatively and postoperatively;[14] its pathogenesis is obscure. There is a high incidence of dyspepsia, of which a substantial proportion is due to peptic ulceration, usually in the duodenum;[15,16] it has been estimated as occurring in 30 per cent of the cases in males. Mental disturbances undoubtedly occur,[17] and the concept of "parathyroid psychosis" has been suggested.[18] Even more bizarre presenting complaints include epileptic sei-

zures, episodes of unconsciousness, headaches, cramps in the feet, ulcerative colitis and many others. When Randall and Keating[19] speak of "serendipity in the diagnosis of primary hyperparathyroidism" they imply that the condition is frequently discovered accidentally.

Biochemical Disturbances

Hypercalcemia—Hypercalcemia is the most important single biochemical finding, but since the normal range of serum calcium varies slightly with the analytic method used, it is impossible to specify an absolute figure above which primary hyperparathyroidism should be diagnosed or suspected. However, any laboratory using a precise and reproducible procedure should usually be able to discriminate between a normal and an abnormal serum calcium concentration[19] (figure 1). Very occasionally, hyperparathyroidism has been diagnosed in the presence of a normal serum calcium when other biochemical findings were positive,[20] but in only one such case has the ionic calcium concentration been measured and it was found to be high.[21] However, since metabolic acidosis reduces the protein binding of calcium and since acidosis may be a feature of primary hyperparathyroidism,[22] it is possible that the administration of alkali in these cases would have revealed the presence of hypercalcemia.

Hypercalcinuria—Hypercalcinuria is not a specific or invariable feature of primary hyperparathyroidism but is rather the result of the raised serum calcium or, more precisely, of the raised ultrafiltrable calcium. In fact, some evidence exists[5] to suggest that the parathyroid hormone tends to lower rather than raise calcium clearance, but this effect usually is more than offset by the rise in the filtered load of calcium.

Assessment of calcium excretion, therefore, is not as important to the diagnosis as is frequently implied; the presence of hypercalcinuria simply confirms the existence of hypercalcemia. Urinary calcium excretion can be evaluated, however, by using the calcium-creatinine ratio (Ca-Cr) either on a random sample or, preferably, on two consecutive 24 hour collections of urine.[23] The Ca-Cr on a free diet is usually raised in primary hyperparathyroidism, particularly in the presence of bone disease (table 2), and if the result is unequivocal further observations on a low-calcium diet are quite superfluous. If a value of about 0.30 is obtained on a free diet, restriction of calcium intake for about one week may serve to establish whether or not true hypercalcinuria is present; the Ca-Cr on a low-calcium diet should not exceed 0.23. If the Ca-Cr is less than 0.28 on the free diet, calcium excretion is normal and further study is unnecessary.

Hypophosphatemia—This finding is less constant than hypercalcemia, and discrimination between normal and abnormal serum phosphate concentrations often is impossible (figure 2); only concentrations below about 2.4 mg. per cent can be regarded as definitely abnormal. However, a low serum phosphate level due to low phosphate intake is associated with a low urine phosphate level, whereas the low serum phosphate of hyperparathyroidism is associated with a relatively high excretion of phosphate. In assessing serum phosphate concentration it is therefore necessary to take into account excretion of phosphate. This can be done most simply by calculating the phosphate-creatinine clearance ratio from the formula:

$$\frac{\text{Urine phosphate} \times \text{serum creatinine}}{\text{Serum phosphate} \times \text{urine creatinine}}$$

(all in milligrams per 100 ml.)

The normal phosphate-creatinine clearance ratio for any given level of serum phosphate can be calculated from the formula 0.055 x serum phosphate –0.07. The extent to which the observed value departs from the normal predicted value is called the phosphate excretion index (PEI), the normal range of which is –0.09 to +0.09.[24] As shown in figure 3, the PEI is raised in primary hyperparathyroidism, but occasional exceptions have been reported in the literature.[25]

The investigation of the renal handling of phosphate can be refined further by use of calcium infusions in doubtful cases. Infusion of calcium gluconate over a four hour period (15 mg. calcium per kilogram of body weight)

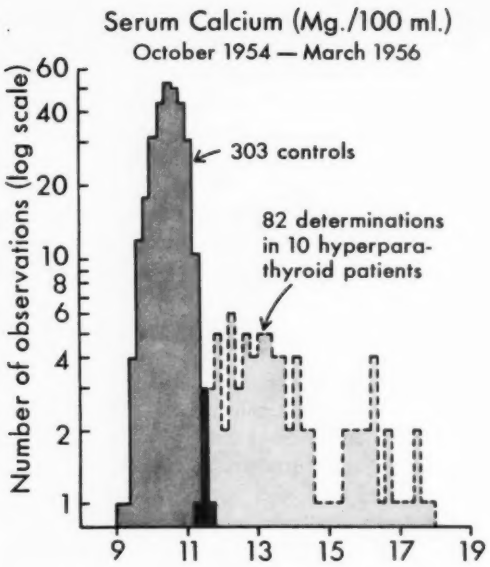

FIGURE 1. Serum calcium concentration in control subjects and patients with primary hyperparathyroidism.

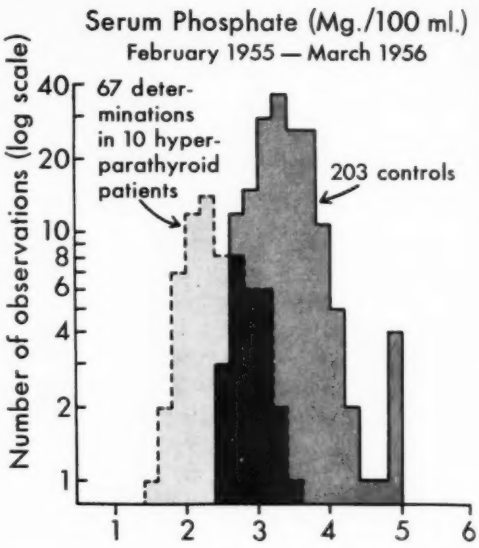

FIGURE 2. Serum phosphate in control subjects and patients with primary hyperparathyroidism.

Figures 1 and 2 reproduced by permission of the authors and publishers from Chambers and associates.[9]

is followed in normal subjects by a fall in urine phosphate excretion to less than half the base level about 12 hours after the infusion[26] (figure 4). This is almost certainly due to suppression of the parathyroid glands. In primary hyperparathyroidism no such fall in urine phosphate excretion occurs, presumably because the tumor is autonomous (figure 4). The discrimination between a normal and an abnormal fall in urine phosphate excretion is obscured if urine is collected for 24 hours instead of every four hours.[27] No great diagnostic value can be attached to the rise in serum phosphate which follows calcium infusion.

TABLE 2

CALCIUM-CREATININE RATIOS IN PRIMARY HYPERPARATHYROIDISM*

OSTEITIS FIBROSA	CALCULOUS DISEASE
0.73	0.39
0.65	0.33
0.53	0.32
0.45	0.30
0.39	0.30
0.32	0.25
0.26	0.23
	0.30
	0.20
	0.15
	0.10

*Some of the data supplied by Dr. I. Anderson.

Impairment of renal concentrating power—An important feature of primary hyperparathyroidism is impairment of renal concentrating power.[28] Even in the presence of a normal glomerular filtration rate, it is unusual for the maximal urinary specific gravity to exceed 1.022. Figure 5 shows that this tubular dysfunction is not due to structural damage but rather is due to functional impairment, since the concentrating power rises substantially after operation in the great majority of patients.

As already mentioned,[11] impaired acidifying power also may be present in primary hyperparathyroidism, but it is not a constant feature and therefore is not likely to be of great diagnostic value. Other biochemical disorders reported in hyperparathyroidism are hypomagnesemia[29] and hypokaliemia;[30] their incidence and diagnostic value are unknown.

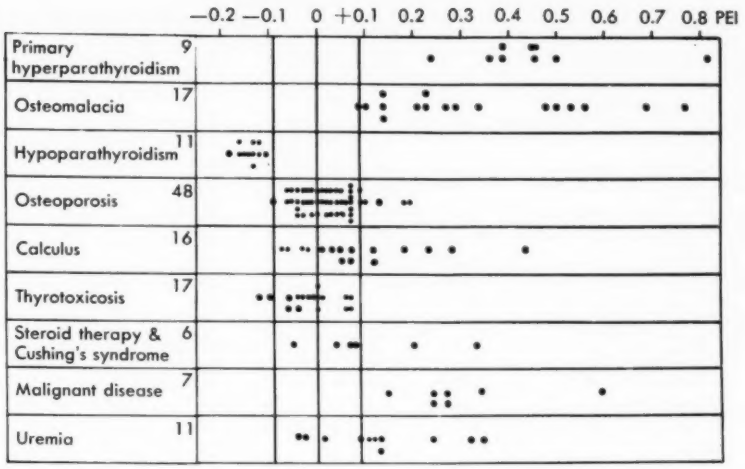

FIGURE 3. Phosphate excretion index (PEI) in parathyroid disorders and other clinical conditions. The horizontal bars show normal range.

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There is preliminary evidence that measurement of the rate of bone formation with chemical strontium[31] or radioactive tracers[32] may be of diagnostic value, since high values are reported in primary hyperparathyroidism.

Radiologic Features

The most common radiologic disorder of the skeleton in primary hyperparathyroidism is osteoporosis which differs in no way from osteoporosis from other causes. This condition can be diagnosed from standard films of the hands, femurs and lumbar spine.[33] In a minority of cases, osteitis fibrosa develops. In these cases the skull presents a "ground-glass" or diffusely mottled appearance (figure 6). Cystic changes may be seen in any part of the skeleton and there may be subperiosteal erosion

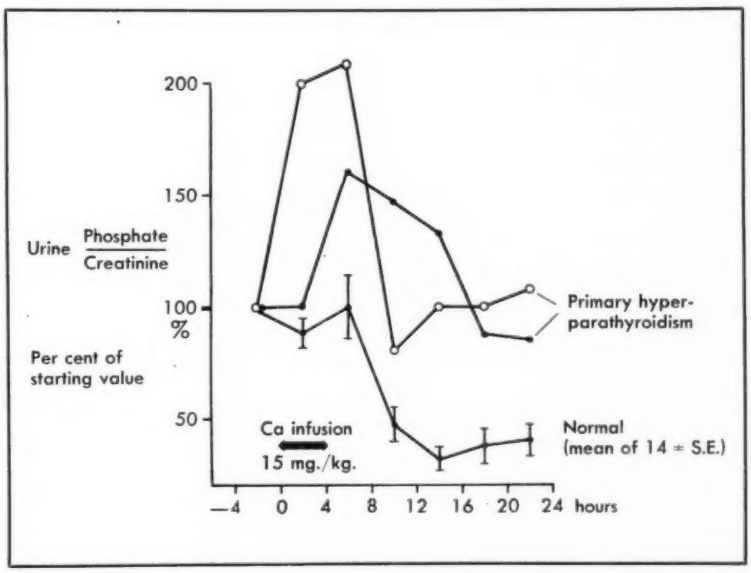

FIGURE 4. Effect of intravenous calcium on urinary phosphate-creatinine ratio in 14 normal subjects and two patients with primary hyperparathyroidism.

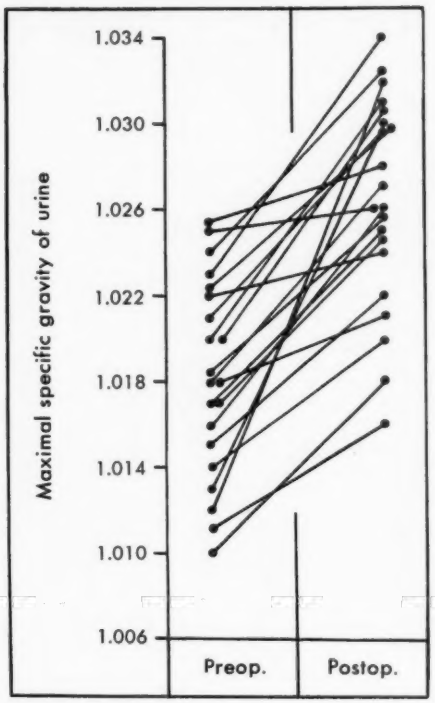

FIGURE 5. Maximal specific gravity of the urine in primary hyperparathyroidism before and after parathyroidectomy. (Based on data of Hellstrom and associates.[28])

either of the phalanges (figure 7) or of the long bones.[34]

In rare cases, rachitic changes have been seen,[35] presumably because the low serum phosphate has reduced the calcium-phosphorus product (Howland-Kramer law) below the critical level for calcification.[1]

Histologic Features

Biopsy of the iliac crest is a simple procedure which can be carried out under local anesthesia with absolute safety.[36] In primary hyperparathyroidism the bone may be normal (figure 8) or it may show osteoporosis (figure 9) or osteitis fibrosa (figure 10).

Types of Tumor

The tumor is most commonly a single adenoma, as shown in table 3, which is based on the series of 207 cases already mentioned.[8]

FIGURE 6. Radiologic appearance of the skull in primary hyperparathyroidism to show diffuse mottling.

Differential Diagnosis

Since primary hyperparathyroidism in association with a normal serum calcium concentration is very rare, or at least rarely diagnosed, the problem of differential diagnosis is essentially the differential diagnosis of hypercalcemia.

Vitamin D poisoning—It should be possible to obtain a history of ingestion of vitamin D in cases of vitamin D poisoning. The serum phosphate level is high rather than low. If the diagnosis is in doubt, a period of observation in the hospital without access to vitamin D results in a fall in serum calcium.

Milk-alkali syndrome—Renal failure is an invariable complication of the milk-alkali syndrome. A recently reported case[37] showed a considerable increase in bone density, both radiologically and histologically, and this may prove to be an important diagnostic feature. Further, withdrawal of milk and alkali results in a fall in serum calcium.

FIGURE 7. X-ray appearance of the hands in primary hyperparathyroidism to show cyst formation, mottling and subperiosteal erosion.

Sarcoidosis—Renal excretion of phosphate usually is normal in sarcoidosis. The cortisone test[38] (100 mg. of cortisone daily by mouth for 10 days) invariably reduces serum calcium to normal (figure 11). In hyperparathyroidism the serum calcium is not affected by this test (figure 12).

Multiple myeloma—The serum calcium concentration may be raised in multiple myeloma, but it should be possible to establish the correct diagnosis from the presence of abnormal protein in the urine or serum, myeloma cells in the marrow, and the high erythrocyte sedimentation rate. Moreover, steroid therapy usually reduces the serum calcium to normal.

Malignant disease—Hypercalcemia in association with malignant disease without bony metastases[22, 39] may present a very difficult diagnostic problem, particularly since renal tubular handling of phosphates may also be abnormal. The biochemical picture may, in fact, be indistinguishable from that of primary hyperparathyroidism. The solution to this problem is not apparent at present.

FIGURE 8. Biopsy of iliac crest to show normal bone in primary hyperparathyroidism (x 15).

FIGURE 9. Biopsy of iliac crest to show osteoporotic bone in primary hyperparathyroidism (x 15).

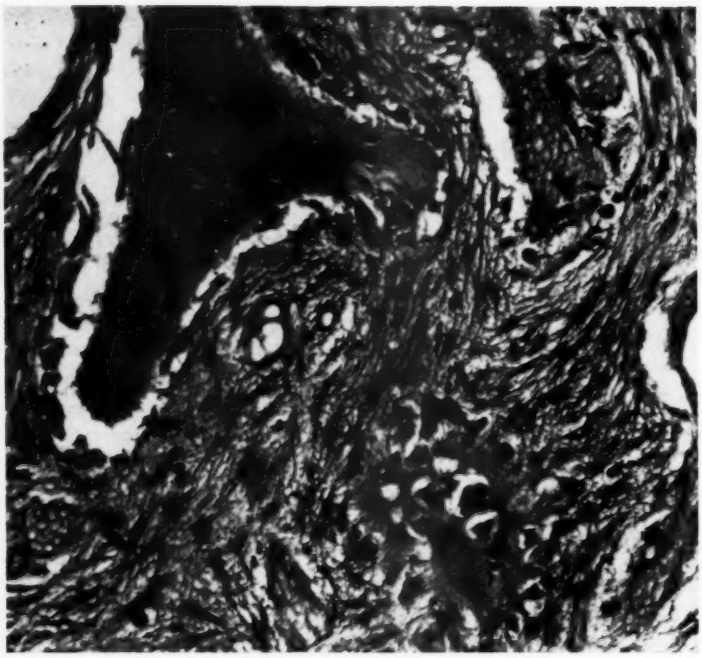

FIGURE 10. Histologic appearance of bone in primary hyperparathyroidism to show osteitis fibrosa.

Parathyroid Adenoma Due to Secondary Hyperparathyroidism

Secondary hyperparathyroidism occurs in vitamin D deficiency (due to loss of the calcemic action of vitamin D on bone) and in glomerular failure (due to direct or indirect stimulation of the parathyroid glands by the raised serum phosphorus).[40] In these conditions, parathyroid hyperplasia or hypertrophy occurs. Recently there have been occasional reports of hypercalcemia due to parathyroid adenoma supervening in these circumstances.[41,42] We have seen two such cases in which all the available evidence suggested that the primary lesion was pyelonephritis, yet a parathyroid adenoma was found at autopsy. It seems possible, therefore, that continuous stimulation of the parathyroid glands occasionally may lead to independent adenoma formation. These cases differ from the usual type of renal failure with secondary hyperparathyroidism in the very great severity of the osteitis fibrosa.

TABLE 3

TYPES OF PARATHYROID TUMOR IN PRIMARY HYPERPARATHYROIDISM*

TYPE OF TUMOR	NUMBER OF CASES	PER CENT
Adenoma	177	86
Multiple adenomas	8	4
Polyglandular syndrome	5	2
Primary hyperplasia	15	7
Carcinoma	2	1

*From Black and Zimmer.[8]

The diagnosis of primary hyperparathyroidism in the presence of advanced renal failure is extremely difficult if not impossible, owing to the depression of serum calcium which follows the elevation of serum phosphorus. However, theoretical considerations and actual observations[40] suggest that depression of serum calcium by an elevated serum phosphorus does not occur until the latter has reached a level of about 6 or 7 mg. per cent. Hypercalcemia due to primary hyperparathyroidism should, therefore, remain detectable until this degree of renal failure has

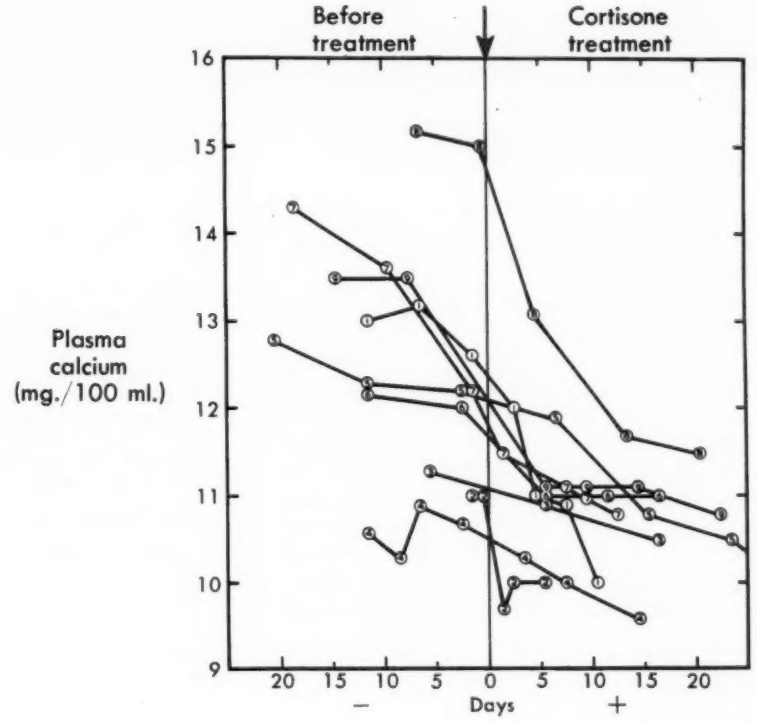

FIGURE 11. Effect of cortisone (50 mg. administered twice daily by mouth for 10 days) on plasma calcium in sarcoidosis.

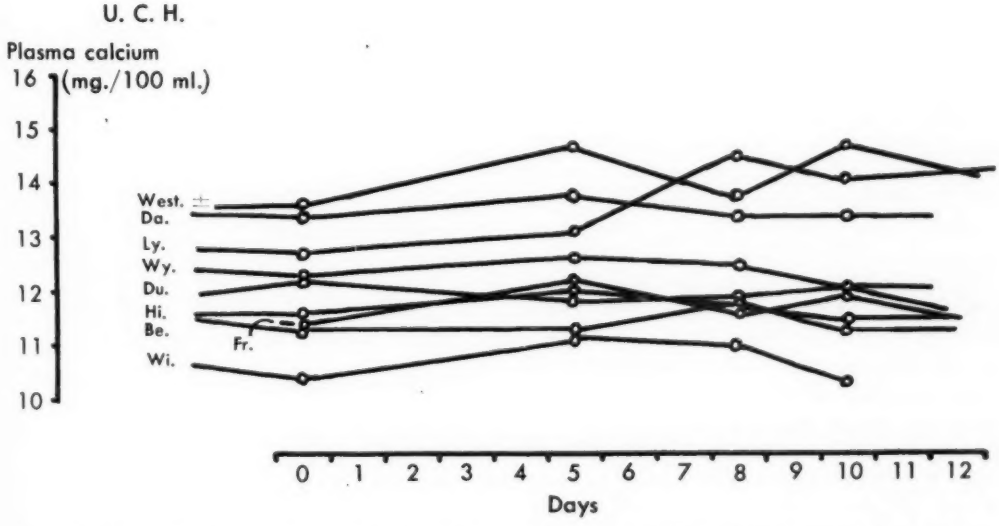

FIGURE 12. Effect of cortisone (50 mg. administered twice daily by mouth for 10 days) on plasma calcium in primary hyperparathyroidism.

Figures 11 and 12 were kindly supplied by Professor C. E. Dent.

been reached, when it is very unlikely that removal of a parathyroid tumor would modify the course of the disease. The problem is therefore somewhat academic.

Treatment

The treatment of primary hyperparathyroidism is, of course, surgical. Discussion of surgical technics is not within the scope of this presentation, nor am I qualified to discuss them. Nevertheless, certain general observations can be made. Something like 99 per cent of the tumors are to be found in the neck.[8] The most experienced surgeons recommend that all four parathyroid glands should be identified during exploration. Frozen sections of suspected tissue should be examined while the operation is in progress. If removal of the adenoma does not cure the patient, further adenomatous tissue is more likely to be found in the neck than in the mediastinum. It is unfortunate that there is a very poor correlation between the size of the adenoma and the severity of the disease, and it is therefore impossible for the surgeon to know what size of tumor he is seeking. Tumors can vary from less than 250 mg. to more than 10 gm.[8]

Conclusions

Primary hyperparathyroidism can no longer be regarded as a very rare disease. Early diagnosis is of immense benefit to the patient and thus a source of satisfaction to the physician, biochemist and surgeon involved. Yet many cases still remain undiagnosed during life,[43] and only a constant awareness of the varying manifestations of the disease can remedy this deficiency.

It has been shown that the diagnosis of primary hyperparathyroidism is still based on indirect procedures which detect biochemical disturbance resulting from excessive excretion of parathyroid hormone. The next objective must be the direct measurement of hormone concentration in tissue fluid. A small start has been made in this direction,[44] but further progress must await the purification and characterization of the parathyroid hormone, on which most encouraging work has been reported recently.[45]

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Subacute Diffuse Thyroiditis

CLINICAL AND LABORATORY FINDINGS IN 24 PATIENTS AND THE EFFECT OF TREATMENT WITH ADRENAL CORTICOIDS

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Because the natural course of subacute diffuse thyroiditis without treatment is extremely variable, it is difficult to evaluate therapy unless it consistently produces rapid, striking improvement; the effectiveness of cortisone and related steroids in this regard is established.

Clinical and laboratory findings in 24 patients are presented. Treatment with adrenal corticoids in 15 patients (prednisolone in 14, cortisone in one) consistently produced rapid and dramatic responses. Relapses occurred in six cases, but permanent remission was achieved in every case.

Therapeutic response to TSH in three cases and to antibiotics in seven cases was not impressive.

SUBACUTE diffuse thyroiditis has interested both clinicians and investigators since de Quervain[1] first described it in 1904. Various names have been given to this syndrome of fever, weakness, sore throat and painful goiter, among them de Quervain's thyroiditis, pseudotuberculous thyroiditis, granulomatous thyroiditis, and giant-cell thyroiditis. The characteristic histologic findings in the involved thyroid gland are granulomas composed of a central mass of colloid with a margin of giant cells and mononuclear cells, and a moderate amount of fibrosis.[2]

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The course of the illness is variable but self-limited, and spontaneous recovery occurs over a period of weeks or months. In the past, treatment has been unsatisfactory with the possible exception of x-ray therapy. More recently, cortisone has been used with dramatic effect on the clinical manifestations of the disease.

The study reported here is an analysis of

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TABLE 1

AGE DISTRIBUTION IN 24 CASES OF SUBACUTE DIFFUSE THYROIDITIS*

AGE (YEARS)	CASES	
	Number	*Per cent*
20 to 30	2	8
30 to 40	7	29
40 to 50	9	38
50 to 60	5	21
60 to 70	1	4

*Range, 27 to 65 years; mean age, 43 years.

the clinical and laboratory findings in 24 cases of subacute diffuse thyroiditis and the results of treatment with adrenal corticoids in 15 patients.

Material and Method

The study group consisted of 24 patients in whom a clinical diagnosis of subacute diffuse thyroiditis had been made. Questionable cases and patients who had goiters that were present prior to the illness were not included. The patients were followed for from 6 to 60 months.

There were 21 women and three men in the group, a ratio of seven to one. Table 1 shows the age distribution; 67 per cent of the patients were between 30 and 50 years of age, and 88 per cent were between 30 and 60 years.

The erythrocyte sedimentation rate was measured by the Westergren method (normal, less than 20 mm. in one hour). Serum chemical protein-bound iodine was measured by the alkali-incineration method of Barker[3] (normal, 3 to 8 μg. per 100 ml.). The uptake of I^{131} by the thyroid was determined 24 hours after a tracer dose[4] had been given (normal, 15 to 50 per cent).

TABLE 2

SYMPTOMS IN 24 CASES OF SUBACUTE DIFFUSE THYROIDITIS

SYMPTOM	NUMBER	PER CENT
Thyroid pain	24	100
Weakness	24	100
Sore throat	19	79
Malaise	19	79
Fever	16	67
Nausea	9	38
Nervousness	9	38
Sweats	9	38
Earache	9	38
"Cold"*	5	20
Headache	4	17
Chills	3	13

*Symptom complex of coryza, sore throat, cough and malaise.

TABLE 3

PHYSICAL FINDINGS IN 24 CASES OF SUBACUTE DIFFUSE THYROIDITIS

FINDING	NUMBER	PER CENT
Thyroid enlargement	24	100
Entire gland	18	75
One lobe	6	25
Thyroid tenderness	24	100
Thyroid firmness	24	100
Tachycardia*	12	50
Pharyngitis	8	33
Thyroid nodularity	6	25
Tremor	4	17
Hyperactivity	2	8
Cervical adenopathy	2	8
Splenomegaly	1	4

*Heart rate over 90 per minute.

Clinical Findings

Table 2 lists the most prominent symptoms. Pain in the lower anterior portion of the neck was present in every case at some time during the illness and, along with sore throat, usually was the main complaint. Pain in the ear usually was described as radiating from the anterior part of the neck to under and behind the ear. An antecedent illness of the "common cold" variety occurred in only five patients (20 per cent). Fever was present in two-thirds of the cases, most often during the early weeks of illness, and generally was low grade. High spiking fever occurred in only four patients.

Table 3 lists the major physical findings. The goiters usually were small or moderate in size. A single thyroid lobe was palpable initially in six patients, and in three of these the other lobe enlarged subsequently. Thus, thyroid involvement was confined to a single lobe throughout the illness in only three patients. The goiters usually were smooth and firm, but in six patients the thyroid gland was finely irregular without prominent nodules.

TABLE 4

LABORATORY FINDINGS IN 19 CASES OF SUBACUTE DIFFUSE THYROIDITIS

PATIENT	HEMOGLOBIN (GRAMS PER 100 ML.)	LEUKOCYTE COUNT	POLYMORPHONUCLEAR CELLS (PER CENT)	LYMPHOCYTES (PER CENT)	SEDIMENTATION RATE (MILLIMETERS IN ONE HOUR)
M.F.	13.5	9,850	77	21	82
I.F.	15.6	9,050	58	41	61
H.G.		10,250	66	29	20
D.T.	12.2	8500	67	31	50
E.W.	12.2	10,450	69	28	101
G.Z.	11.9	7600	82	18	65
J.K.	10.5	7,950	68	30	24
F.M.	11.3	9,350	62	32	
D.S.					48
E.K.	11.9	8,750	60	35	43
L.M.	15.1	15,500	80	17	71
L.C.	12.1	7,350	63	34	106
F.H.		7500	64	32	17
E.C.	10.5	10,400	74	23	65
M.C.					28
R.F.	12.5	6300	70	27	111
R.C.	12.6	11,700	86	13	57
N.H.	12.6	8900	77	20	29
M.M.	11.9	8800	66	33	30
Mean	*12.4*	*9,396*			*56*

Pain on palpation of the thyroid usually was marked and could be elicited by turning the head, swallowing and coughing. Pharyngitis, when present, consisted of redness without exudate or edema. Hyperactivity and tremor were not marked, and in no case was a diagnosis of thyrotoxicosis considered seriously.

Laboratory Findings

The total leukocyte count was normal (less than 10,000 cells per cubic millimeter) in 12 of 17 patients, and in only two was it more than 11,000 cells (table 4). The erythrocyte sedimentation rate was abnormal in 16 of 18 patients (89 per cent). In 10 patients the sedimentation rate was 50 mm. in one hour, or more, but in only three was it over 100 mm. in one hour.

Urinalyses, serologic studies and chest x-rays all yielded negative results. Throat cultures were made in five cases, and the only pathogen found was beta hemolytic *Streptococcus* in one patient.

One patient (J.K.), a 28 year old woman, had a transiently abnormal electrocardiogram with multiple T wave changes and chest pain suggestive of myocarditis.

Thyroid Function Tests

Thyroid function tests performed during the acute phase of illness in 17 patients are summarized in table 5. Thyroid uptake of I^{131} was low in all but two patients (J.K., M.M.) and 5 per cent or less in 10 patients. Serum chemical protein-bound iodine levels were elevated in four of five patients tested.

Stimulation of the thyroid gland with pituitary thyrotropin was attempted in three patients (table 6). There was no significant increase in thyroid uptake of I^{131}, but a small increase in serum chemical protein-bound iodine concentration occurred.

Treatment With Adrenal Corticoids

Fifteen patients were treated with corticosteroids. Prednisolone was used in 14 patients and cortisone in one patient, and for purposes of this analysis these 15 cases were considered together. Usually, 25 to 40 mg. of prednisolone daily was given for the first two days, following which an attempt was made to reduce the dosage rapidly over a period of one week until a maintenance dosage of 10 to 15 mg. daily was reached. In most cases, after

TABLE 5

THYROID FUNCTION TESTS IN 17 CASES OF SUBACUTE DIFFUSE THYROIDITIS

PATIENT	THYROID I^{131} UPTAKE (PER CENT AT 24 HOURS)	SERUM PROTEIN-BOUND IODINE (MICROGRAMS PER 100 ML.)	B.M.R. (PER CENT)
I.F.	5		
F.W.	5		
G.Z.	2		
J.K.	15	6.7	
E.K.	11		
L.C.		8.8	
E.C.	1	8.8	+15
M.C.	10		
R.F.	1	12.2	
R.C.	1	9.8	
N.H.	11		
R.M.	0		
G.M.	2		+17
D.R.	2		
L.G.	12		−3
I.Fe.	0		
M.M.	24		
Mean	*6*		

three to four weeks of therapy the dosage was reduced further and the drug was discontinued after seven days. If symptoms recurred when the dosage was reduced, the dosage was increased to the previous level and continued for a longer period. If relapse occurred after discontinuation of prednisolone, a second but shorter course of treatment was given. Twelve of the 15 patients also received an intramuscular injection of 60 to 80 units of depot ACTH on the first day of treatment.

All 15 patients responded rapidly and dramatically to treatment (table 7). In almost every case the systemic symptoms of thyroiditis had subsided and the thyroid tenderness and pain had disappeared after 24 to 48 hours. The thyroid enlargement subsided within 14 days in all but three patients, and in over half the cases the goiters disappeared within seven days. In one patient (F.H.) the goiter rapidly decreased in size but did not disappear entirely until two months after institution of treatment, and in two patients (F.M., E.K.) small, nontender, firm and irregular goiters were still palpable six and nine months, respectively, after treatment. A longer period elapsed before remission of symptoms and disappearance of thyroid tenderness and enlargement in the three patients (F.H., R.C., L.C.) who did not receive ACTH. After treatment was begun, the mean duration of symptoms was 1.7 days, of thyroid tenderness 1.7 days, and of thyroid enlargement 10.5 days. The duration of illness before institution of prednisolone therapy varied from 7 to 56 days and did not appear to influence the immediate response to treatment. The total length of treatment in the 15 patients ranged from 12 to 72 days (mean, 40 days).

Six patients (40 per cent) had a relapse either while receiving maintenance doses of prednisolone or after discontinuing treatment (after 1 to 14 days) (table 8). Four patients relapsed once, and two patients relapsed twice. The relapses generally were mild and mani-

TABLE 6

EFFECT OF TSH* STIMULATION ON THE THYROID UPTAKE OF I^{131} IN THREE PATIENTS DURING THE ACUTE PHASE OF SUBACUTE DIFFUSE THYROIDITIS

PATIENT	DOSAGE OF TSH	THYROID UPTAKE OF I^{131} (PER CENT OF DOSE AT 24 HOURS)		SERUM PROTEIN-BOUND IODINE (MICROGRAMS PER 100 ML.)	
		Before TSH	*After TSH*	*Before TSH*	*After TSH*
E.C.	10 units daily x 4	1	2	8.8	11.3
R.F.	10 units daily x 3	1	4	12.2	14.6
R.C.	10 units daily x 4	1	1		

*Pituitary thyroid-stimulating hormone (Armour).

TABLE 7

EFFECT OF TREATMENT WITH ADRENAL STEROIDS* ON THE CLINICAL COURSE OF SUBACUTE DIFFUSE THYROIDITIS IN 15 PATIENTS

PATIENT	DURATION OF ILLNESS BEFORE TREATMENT (DAYS)	TOTAL DAYS TREATED	DURATION OF SYMPTOMS AFTER BEGINNING OF TREATMENT (DAYS)			RELAPSES AFTER TREATMENT
			Symptoms	*Thyroid tenderness*	*Thyroid enlargement*	
M.F.	7	24	1	1	5	0
F.H.	7	24	2	2	56	0
R.C.	7	42	3	1	10	0
M.M.	12	32	1	1	1	0
N.H.	14	31	1	1	5	0
J.K.	16	12	1	1	3	0
F.M.	20	59	2	3	p†	2
L.C.	21	53	2	2	14	1
E.W.	21	60	1	1	4	1
D.S.	28	36	3	3	10	0
I.F.	30	39	1	1	14	0
M.C.	42	59	1	1	1	2
G.Z.	42	72	1	1	7	1
H.G.	56	23	1	1	7	0
E.K.	56	32	5	5	p‡	1
Mean	*25*	*40*	*1.7*	*1.7*	*10.5*	

*One patient (F.H.) received cortisone. The others received prednisolone.

†Persistent small, nontender goiter six months after treatment.

‡Persistent small, nontender goiter nine months after treatment.

fested by a return of thyroid tenderness, slight enlargement of the gland and, in a few cases, recurrence of fever and malaise. In each case, reinstitution of prednisolone or increase in dosage resulted in prompt remission of all signs and symptoms of thyroiditis. A permanent remission was finally achieved in every case. The final course of prednisolone leading to a sustained remission was shorter than the course of treatment prior to relapse (mean, 14 days, compared with 36 days).

A comparison of patients who had a sustained remission and those who relapsed after the first course of treatment revealed several differences (table 9). The mean duration of illness before treatment was greater in the relapse group (34 days, compared with 20 days). The mean duration of the first treat-

TABLE 8

RELAPSE OF SUBACUTE DIFFUSE THYROIDITIS DURING OR AFTER TREATMENT WITH ADRENAL STEROIDS

PATIENT	FIRST RELAPSE		SECOND RELAPSE		FINAL TREATMENT (DAYS)	TOTAL DAYS OF TREATMENT
	Days treated	*Days after treatment*	*Days treated*	*Days after treatment*		
F.M.	28	*	21	3	10	59
E.W.	40	7			20	60
L.C.	33	*			20	53
M.C.	35	*	17	*	7	59
G.Z.	60	14			12	72
E.K.	19	1			13	32
Mean	*36*		*19*		*14*	*56*

*Relapse occurred when dosage of prednisolone was decreased to 5 mg. daily.

TABLE 9

COMPARISON OF PATIENTS WHO HAD A REMISSION WITH THOSE WHO RELAPSED FOLLOWING FIRST COURSE OF TREATMENT WITH ADRENAL STEROIDS

PATIENT	DURATION OF ILLNESS BEFORE THERAPY (DAYS)	DAYS TREATED, FIRST COURSE	TOTAL DAYS TREATED	THYROID LOBES ENLARGED
REMISSION AFTER FIRST COURSE OF TREATMENT				
M.F.	7	24	24	Both
F.H.	7	24	24	Both
R.C.	7	42	42	One
M.M.	12	32	32	Both
N.H.	14	31	31	One
J.K.	16	12	12	Both
D.S.	28	36	36	Both
I.F.	30	39	39	Both
H.G.	56	23	23	Both
Mean	*20*	*29*	*29*	*78 per cent, both lobes*
RELAPSE AFTER FIRST COURSE OF TREATMENT				
F.M.	20	28	59	Both
E.W.	21	40	60	Both
L.C.	21	33	53	Both
M.C.	42	35	59	One
G.Z.	42	60	72	One
E.K.	56	19	32	Both
Mean	*34*	*36*	*56*	*67 per cent, both lobes*

ment period was actually longer in the relapse group (36 days, compared with 29 days). The total duration of treatment was twice as long in the relapse group because of the added days of therapy after relapse. Both of the patients in the relapse group in whom a single thyroid lobe was involved initially had recurrence of thyroiditis in the other thyroid lobe; however, two patients in the remission group also had only unilateral involvement of the thyroid gland and did not relapse.

No complications of adrenal corticoid therapy were encountered.

Treatment With TSH

Three patients were given pituitary thyrotropin during the acute phase of thyroiditis (table 10). The effect on thyroid uptake and serum protein-bound iodine has been discussed (table 6). One patient (R.C.) became worse following administration of TSH, with increase in thyroid pain, weakness, fever and malaise. Nine days after the administration of TSH, she was treated with prednisolone and had a prompt remission. The response in the other two patients was gradual, and it is very likely that it represented a spontaneous remission rather than an effect of TSH.

Treatment With Antibiotics

Seven patients received penicillin or tetracycline for varying periods (4 to 21 days) during the early phase of illness. Improvement did not occur and the course of the thyroiditis was not altered in any of these patients.

Hypothyroidism Following Subacute Thyroiditis

Three patients (R.F., F.H., M.M.) became hypothyroid two, two and four months, respectively, after remission of thyroiditis. One had received TSH for three days, and the other two had received prednisolone for 24 and 32 days. All three patients still required

TABLE 10

EFFECT OF TREATMENT WITH TSH ON THE CLINICAL COURSE OF SUBACUTE DIFFUSE THYROIDITIS IN THREE PATIENTS

PATIENT	DOSAGE OF TSH	DURATION OF ILLNESS BEFORE TREATMENT (DAYS)	DURATION OF SYMPTOMS AFTER TREATMENT BEGUN (DAYS)			CLINICAL RESPONSE
			Symptoms	*Thyroid tenderness*	*Thyroid enlargement*	
E.C.	10 units daily x 4	21	1	21	56	Gradual
R.F.	10 units daily x 3	28	3	14	14	Gradual
R.C.	10 units daily x 4	7				None*
Mean			*2*	*18*	*35*	

*R.C. had no response to TSH, and after nine days treatment with prednisolone was begun.

thyroid extract therapy 12, 46 and 56 months, respectively, after the appearance of hypothyroidism. This represents an incidence of hypothyroidism of 12.5 per cent following subacute diffuse thyroiditis in this series.

Discussion

The much higher incidence of subacute diffuse thyroiditis in women and the more frequent occurrence between the ages of 30 and 50 years were evident in this study. Skillern, Nelson and Crile[5] reported a preponderance of women of almost four to one in a group of 66 patients. Two-thirds of the patients studied by Robbins and co-workers[6] were women, and the average age was 43.7 years.

The prototype of a case of subacute diffuse thyroiditis might be described as that of a 40 year old white woman with moderate fever, malaise and weakness of about three weeks' duration who complains rather bitterly of vague, persistent pain in the anterior neck and throat, radiating to the ears and aggravated by rotation of the head and swallowing, and who is found on examination to have a firm, smooth, very tender goiter and perhaps mild tremor, sweating and tachycardia. This basic pattern varied in degree but was consistently found in patient after patient.

The impression that an upper respiratory infection usually precedes the occurrence of subacute thyroiditis was not substantiated in our patients. The illness often has an insidious beginning, and since the major pathologic process involves the neck, what the patient may interpret as a "cold" turns out to be, on careful questioning, the early manifestations of the thyroid inflammatory process. The thyroiditis is often not diagnosed and may be treated with antibiotics and symptomatic measures as a particularly stubborn pharyngitis, the patient eventually going into a spontaneous remission after a period of weeks. Routine palpation of the thyroid gland in every patient complaining of a sore throat would undoubtedly result in recognition and treatment of many more cases.

Laboratory studies are of considerable help in confirming the clinical diagnosis. The leukocyte count and the hemoglobin level usually are normal. Skillern and associates[5] reported that 11 (17 per cent) of their 66 patients had a normochromic, normocytic anemia (hemoglobin level less than 11 gm. and as low as 8.3 gm.). Among our patients, only two had hemoglobin values below 11 gm. The thyroid uptake of radioiodine usually is low during the course of subacute thyroiditis, often being less than 5 per cent at 24 hours.[5-10] This was well demonstrated in our study. An uptake of I^{131} by the thyroid in the normal range during the acute phase of the illness should cast suspicion on the accuracy of the diagnosis. The thyroid uptake usually returns to normal with-

in 12 weeks after recovery.[6,8-10] The serum chemical protein-bound iodine concentration frequently is in the hyperthyroid range during subacute thyroiditis.[6,8-10] Towerly[8] found a mean protein-bound iodine level of 8.6 μg. in a group of 20 patients, and in 10 the values were between 9.1 and 12.7 μg. Four of five patients tested in our series had protein-bound iodine values above 8 μg.

Robbins and associates[6] reported a significant (but less than normal) increase in thyroid uptake of I^{131} in six patients with subacute thyroiditis who were given 25 to 30 mg. of TSH daily for one to five days (before TSH, 0.4 to 2.3 per cent; after TSH, 6.2 to 37.1 per cent). A rise into the normal range occurred in only two patients. Czerniak and Steinberg[9] studied one patient with TSH and found an increase in uptake of I^{131} from 3 to 40 per cent 48 hours after a single injection. They interpreted this to indicate that pituitary production of TSH is low during subacute thyroiditis. Skillern and co-workers[5] reported TSH studies in 12 patients and found no response in 10 and a low response in two (before TSH, 9.5 per cent average; after TSH, 11.6 per cent average). The results of TSH stimulation in our cases, in which the dosage was similar to that used by Robbins and associates, indicated unresponsiveness of the goiter of subacute thyroiditis.

Ingbar and Freinkel,[11] studying thyroid hormonal turnover rates in subacute thyroiditis with radioiodine, concluded that a glandular defect in hormonal iodine storage existed, and this was supported by the observation of a diminished or absent 24 hour accumulation of I^{131} by the thyroid despite normal or increased concentrations of protein-bound and butanol-extractable (thyroxin) I^{131} and an abnormally early peak of butanol-extractable I^{131} in the serum following a tracer dose. They also demonstrated in the plasma of three subjects abnormally large fractions of organically bound I^{131} with solubility characteristics of thyroglobulin, and in two patients large discrepancies between the concentrations of protein-bound and butanol-extractable stable (I^{127}) iodine, indicating an abnormal release of organic iodine compounds by the thyroid.

It is difficult to accept the theory[9] that release of large amounts of thyroxin during the inflammatory phase of thyroiditis and the subsequent rise in the level of thyroid hormone in the blood result in a suppression of pituitary production of TSH and, consequently, a decrease in thyroid uptake of I^{131}. Under these circumstances a normal uptake response by the thyroid to administered TSH should occur, rather than the negligible or suboptimal responses which have been observed. It is more likely that the low thyroid uptake reflects the inflammatory injury to thyroidal acinar cells, producing a failure of the iodine-trapping and iodine-storage mechanisms in the gland.

Because of the great variability in the natural course of subacute thyroiditis without treatment, it is difficult to evaluate therapy unless it consistently produces rapid and striking improvement. Antibiotics have been discarded as completely ineffective in subacute thyroiditis. The antithyroid drugs thiouracil and methimazole (TAPAZOLE®) have been reported to produce a remission,[12-14] but the response has been slow and inconsistent and it is very likely that it represents spontaneous fluctuations in the disease. The antithyroid drugs have in general been discredited as an effective treatment of subacute thyroiditis. X-ray therapy probably does influence the course of the disease, but the responses often are slow, failures common, and relapses frequent. Crile and Schneider[15,16] have, in the past, advocated 600 to 1000 r delivered to the thyroid over a one week period and have reported remission of thyroiditis in two to six weeks. They stated that this dosage does not cause permanent damage to the thyroid gland; however, a high incidence of hypothyroidism has been reported following x-ray therapy.[12] Osmond and Portmann[17] treated 55 cases with one course of 400 to 600 r and produced a "satisfactory remission" in 40 patients. Allen and Reeves[18] administered 500 to 1000 r to 15 patients and observed relapses in 27 per cent; remission did not occur for at least two weeks. Thyroidectomy has been performed in some cases,[2,14] but it is difficult to believe that such radical treatment is ever indicated in this disorder. Robbins and his group studied

the therapeutic effects of TSH in six patients and reported that four had definite subjective improvement, one had equivocal benefit, and one patient became worse. Four of those who improved had relapses within seven days. The therapeutic response to TSH in our three cases was not impressive.

The effectiveness of cortisone and related steroids in producing a prompt, complete remission of subacute thyroiditis is established. I was able to collect 52 cases treated with adrenal steroids from the literature since 1952, when the first cortisone-treated patients were reported.[5,15,19-26] Failure to respond was reported in only one case,[19] that of a patient who received adequate amounts of cortisone for 18 days without evidence of improvement and was finally treated successfully with x-ray therapy. In the other 51 patients a rapid, dramatic remission followed initiation of treatment. Sustained remissions were produced with as little as seven days of therapy.[20] Salassa[21] reported that the treatment period in 24 patients varied from nine days to six months with an average of eight weeks. Most of the patients were treated with cortisone, but Skillern and associates[5] used prednisolone in six patients and recommended an initial dosage of 20 mg. daily with gradual reduction in dosage at 7 to 14 day intervals and discontinuance at 28 days. Werner[22] obtained a much more rapid remission with ACTH than with cortisone.

The great variation in length of treatment necessary to produce a sustained remission was also apparent in our cases. Relapses may be expected in perhaps 40 per cent of patients when dosage is reduced or treatment is stopped. The relapses, however, are very mild and easily and rapidly controlled by reinstitution of steroid therapy, usually for a shorter period.

The dosage of prednisolone must be tailored to the individual patient, but a reasonable dosage schedule would be 30 mg. the first day, 25 mg. the second day, and 20 mg. the third through the seventh day. Dosage is then reduced by 5 mg. every seven days until treatment is discontinued on the twenty-ninth day. If symptoms recur when the dosage is reduced, the dosage is increased to the previous level and reduction is delayed for one week. If a relapse occurs after treatment is discontinued, a second course should be given, usually shortened to 14 to 21 days. Administration of 60 units of depot ACTH on the first day of therapy results in a remission of symptoms within eight hours in most cases. Our experience with patients who had relapses suggests that if a patient is ill longer than 30 days before treatment a somewhat longer course of therapy should be given, perhaps six weeks.

Complications and late residuals of subacute thyroiditis are uncommon. McConahey and Keating[7] reported that six of 18 patients became hypothyroid following recovery. Persistent hypothyroidism developed in three of our patients. Crile[16] has not noted hypothyroidism following subacute thyroiditis. Only one of 27 patients treated by thyroidectomy for subacute thyroiditis became hypothyroid.[2] A persistent goiter after recovery is unusual, occurring in only two of our patients.

Perloff,[27] Sheets[28] and Volpe and associates[10] reported the occurrence of hyperthyroidism within one year after recovery from subacute thyroiditis. No other reports of this nature have appeared, and certainly this sequence must be rare.

Cardiac involvement in subacute thyroiditis has not been reported. The abnormal electrocardiogram and chest pain in one of our cases was interpreted as evidence of myocarditis associated with subacute diffuse thyroiditis. It is possible that if electrocardiograms were made more frequently in this disease it would be found that myocardial involvement occurs more commonly than is appreciated at present.

Summary

Clinical and laboratory findings in 24 patients and the results of therapy with adrenal corticoids in 15 patients with subacute diffuse thyroiditis are presented. The disease occurred seven times more frequently in women than in men, and most commonly between the ages of 30 and 50 years. Thyroid enlargement, pain and tenderness, weakness, sore throat, malaise and fever were the most frequent manifestations of the disease. The sedimentation rate

and the serum protein-bound iodine concentration usually were elevated, and thyroid uptake of radioiodine usually was very low and did not respond to stimulation with TSH. Prednisolone therapy resulted in prompt remission in every case, although mild transient relapses occurred in six of 15 cases. Complications were limited to hypothyroidism in three patients, small persistent goiters in two patients, and a transient myocarditis in one.

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Treatment of Hyperthyroidism With Antithyroid Drugs

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When the requirements of proper dosage, duration and distribution of administration are met, propylthiouracil and similar agents are effective, safe, inexpensive and convenient in treatment of hyperthyroidism. Hyperthyroidism in youth and in pregnancy presents special problems, and antithyroid drugs are the treatment of choice. We believe that the uncertainty of the long-term effects of radioiodine warrants the use of antithyroid drugs in most young adults with hyperthyroidism.

It has now been 18 years since Astwood[1] introduced antithyroid drugs for the treatment of hyperthyroidism. The experience of nearly two decades permits an accurate evaluation of the problems encountered, the precautions to be observed, and the results to be expected in the use of these agents. In the last decade the pendulum of therapeutic preference has swung toward the use of radioiodine treatment in hyperthyroidism and away from the use of antithyroid drugs. We believe it is time for the pendulum to swing back to a point at which antithyroid drugs are used in a larger portion, indeed the bulk, of cases of hyperthyroidism. We shall discuss the practical use of antithyroid drugs as the primary treatment of hyperthyroidism.

Mode of Action of Antithyroid Drugs

The first objective in the treatment of hyperthyroidism is to relieve the signs and symptoms produced by the effects on the tissues of excessive amounts of circulating thyroid hormone. All forms of treatment of this disease are aimed at diminishing to normal the amount of thyroid hormone released by the gland and thus restoring metabolic equilibrium. Antithyroid drugs achieve this effect by interfering with the processes of synthesis of thyroid hormone. An outline of the steps in the biosynthesis of thyroid hormone and of the sites at which antithyroid drugs are inhibitory is shown in figure 1.

Normal thyroid cells have the ability to concentrate inorganic iodide ion to a level about 25 times the level of plasma, and in hyperthyroidism a several hundredfold concentration of iodide occurs. Before entering into organic synthetic processes, the iodide ion is

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oxidized to an active form (shown in figure 1 as iodine, although this probably is an oversimplification). Active iodine then reacts with tyrosine to form monoiodotyrosine, and addition of a second atom of iodine produces diiodotyrosine. Condensation of two molecules of diiodotyrosine leads to the formation of thyroxin. The other active thyroid hormone, 3, 5, 3′-triiodothyronine, may be formed either by condensation of a molecule of diiodotyrosine and one of monoiodotyrosine or by deiodination of thyroxin.

Of the substances elaborated by the thyroid gland, only thyroxin and triiodothyronine have significant hormonal effects, the latter being several times more active than the former. The thyroid hormones are stored in the colloid as part of molecules of thyroglobulin; in fact, tyrosine already may be bound to thyroglobulin before iodination occurs, the protein molecule serving as a template for synthesis and as a carrier for transportation of thyroid hormone within the cell. Before hormone is released into the blood the thyroglobulin molecule is broken down enzymatically and thyroxin and triiodothyronine pass into the blood, where they are bound to plasma protein for transport to the tissues.[2]

Antithyroid drugs which have been proved clinically useful can be divided into two groups depending on the mechanism by which they interfere with hormone synthesis. Thiocyanate and perchlorate act on the iodide-trapping mechanism, preventing the gland from concentrating iodide ion. Thiocyanate has too brief a duration of action to be useful clinically, but perchlorate has been tried successfully by a few investigators.[3,4] (A recent paper[5] concludes that perchlorate is the treatment of choice in hyperthyroidism, but the assessment of the drug is incomplete, particularly with regard to its ability to induce long-lasting remissions.) Further experience with this agent is needed before its place in the treatment of hyperthyroidism can be adequately evaluated.

The larger, more useful group of antithyroid drugs consists of derivatives of thiourea. These substances act to inhibit organic binding of iodine, but the mechanism of this inhibition is still uncertain. They clearly do not interfere with the iodide-concentrating mechanism; in fact, the thyroid-serum ratio of iodide is enhanced after the administration of propylthiouracil. Astwood,[6] after reviewing the evidence in regard to the site of action of antithyroid drugs, concluded that the most likely effect was inhibition of peroxidase, an enzyme believed to be responsible for oxidizing iodide to iodine. Subsequent evidence, however, suggests that the action is more complex than simple inhibition of this enzyme, since the synthesis of diiodotyrosine, triiodothyronine and thyroxin is inhibited to a much greater extent than is the formation of monoiodotyrosine.[7,8]

A large number of compounds of this class have been studied for their antithyroid action, but only a few have been tested extensively enough to warrant their use in treatment. For reasons of toxicity and unpleasantness of administration, thiouracil and thiourea, the agents initially used for therapy, have been supplanted by derivatives.

Figure 2 shows the structure of the parent compounds and of those drugs which have had sufficient clinical trial to demonstrate satisfactory thyroid suppression in doses associated with a low incidence of toxic reactions. The potency varies among the drugs, 100 mg. of propylthiouracil or methylthiouracil being equivalent to about 10 mg. of methylmercaptoimidazole or carbethoxythiomethylglyoxaline. Here, as in other types of therapy, the relative potency of one drug with respect to another does not per se indicate a therapeutic advantage of the more potent drug, but only does so if a decrease in toxic reactions or side

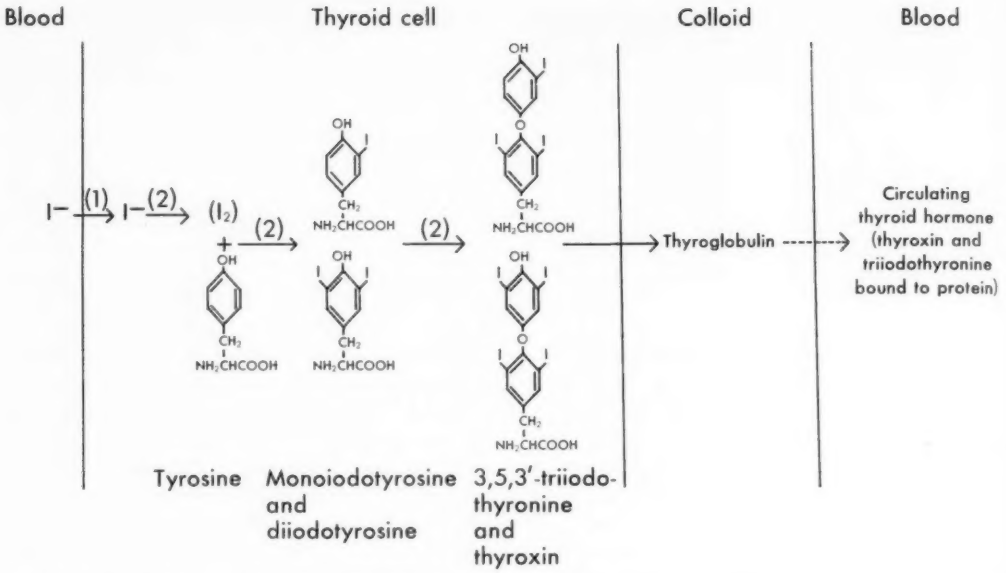

FIGURE 1. Synthesis of thyroid hormone and sites of action of antithyroid drugs. (1) Site of action of perchlorate and thiocyanate. (2) Sites of probable action of thiourea and thiouracil derivatives.

effects accompanies the lower dosage. There is little to choose from in this respect among the agents just mentioned. More information has been accumulated concerning propylthiouracil than other antithyroid drugs, and our experience has largely been with this agent; its use will be discussed hereafter.

Considerations in the Clinical Use of Antithyroid Drugs

Effective use of any powerful pharmacologic substance depends on the proper adjustment of the dose, distribution and the duration of administration. Good results in the treatment of hyperthyroidism require consideration of each of these factors; their neglect accounts for many of the "treatment failures" with propylthiouracil and other antithyroid drugs.

Dosage—The initial dosage of propylthiouracil is usually between 300 and 400 mg. daily. Higher initial doses may be used for patients who require more rapid and more uniform suppression of thyroid function. Patients with thyrotoxic cardiovascular disease, with thyrotoxic crisis, with a concomitant infection, or with other debilitating disease may be given as much as 1200 mg. a day until improvement in their hyperthyroid manifestations occurs. However, as will be mentioned in the discussion of toxic reactions, higher doses carry an increased risk of toxicity, and in most cases of uncomplicated hyperthyroidism nothing is gained by prescribing more than 400 mg. of propylthiouracil a day. With the degree of suppression obtained with this amount of the drug, amelioration of the patient's symptoms usually begins within two weeks after starting treatment.

Distribution—When administered orally, propylthiouracil is absorbed rapidly from the intestinal tract and exerts its total effect within a period of four hours. It has been shown that 200 mg. of propylthiouracil every three hours is more effective in suppressing thyroid function than 400 mg. every six hours.[9] Successful antithyroid therapy can be and usually is conducted with the drug distributed at six or eight hour intervals, but the preceding information suggests the importance of spacing the individual doses as evenly as possible throughout the 24 hours. Sleep need not be interrupted, but the patient should be instruct-

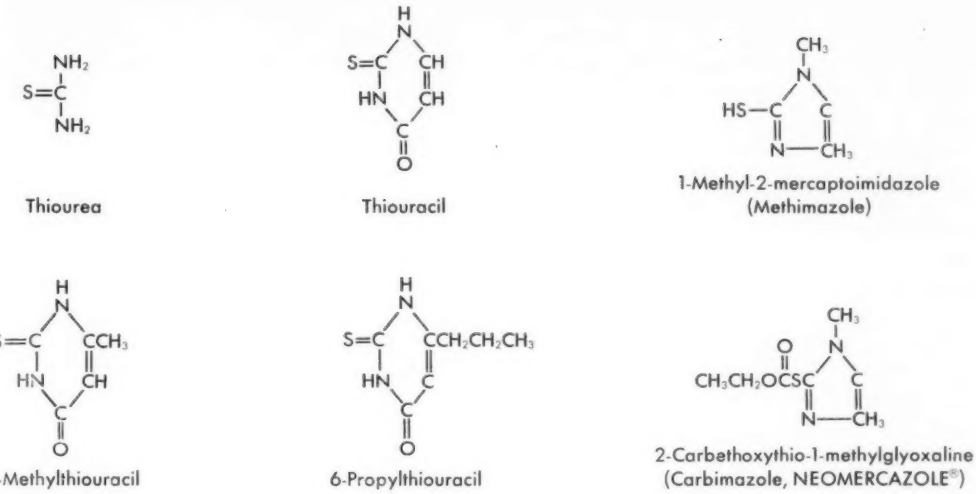

FIGURE 2. Parent compounds and clinically useful antithyroid drugs.

ed to take propylthiouracil before going to bed and immediately on arising; the remaining one or two doses should then be spaced so as to provide even intervals between doses during the waking hours. In severely ill patients, requiring rapid control of their disease, administration of 100 mg. every two hours may be advisable.

Duration—Numerous studies attest to the importance of prolonged duration of treatment with antithyroid drugs in order to obtain a high percentage of permanent remissions. The fact that a patient is clinically and chemically euthyroid for the majority of the period of treatment does not lessen the importance of prolonged maintenance of propylthiouracil for good long-term results. It is important that the patient understand at the start of treatment that he must take the drug for months regardless of the rapidity with which his symptoms subside; failure of the patient to understand this aspect of treatment promotes discouragement and unprescribed discontinuation of the medication. Some patients treated for only a few months obtain permanent remissions from their disease; others, who are often clinically indistinguishable from members of the first group, require many months of treatment for the same results. Since there is no clinical or laboratory means of separating these two groups at the start of treatment, it is our practice to give propylthiouracil for a minimum of 12 months.

The best indication of successful inhibition of the hyperthyroid process is clinical improvement in the patient's symptoms and signs. Nervousness, diarrhea, increased heat production, tremor and tachycardia begin to subside and weight gain begins within two weeks after starting treatment in most patients. As a rule the eye manifestations are the slowest features to improve. It remains our impression that full control of hyperthyroidism with antithyroid agents gives most satisfactory results in regard to ocular manifestations. An occasional patient may not improve until 8 to 12 weeks after starting treatment with 300 or 400 mg. of propylthiouracil, and rarely a larger dosage is necessary to suppress the thyroid gland.

Laboratory follow-up—Of the two common laboratory tests of thyroid function, the PBI and the 24 hour I^{131} uptake, only the former is of value in following the course of treatment. As the disease subsides the PBI falls to normal and to below normal if hypothyroidism intervenes. In regard to the I^{131} uptake, it has been pointed out that propylthio-

uracil is a drug with a short duration of action, and during the course of a day the state of function of the gland varies from markedly suppressed to uninhibited unless propylthiouracil is given every four hours or oftener. Therefore, in a patient receiving the drug at the customary six or eight hour intervals, the I^{131} uptake may be subnormal, normal or elevated, depending on the phase of glandular suppression present at the time the radioiodine in the thyroid is measured.

Factors in prognosis—Treatment as described results in permanent relief of hyperthyroidism in about two-thirds of patients. The remainder have a recurrence of their disease, usually within six months after stopping propylthiouracil. Many factors have been studied to help predict relapse. Only two are of sufficient prognostic importance to warrant mention. A patient whose goiter diminishes in size after starting treatment is likely to have a lasting remission; in a patient whose goiter does not change in size, it may be advisable to continue treatment for longer than a year. The second factor, of lesser significance, is the presence of a diffuse versus a nodular goiter, the former having a better long-term prognosis for successful treatment than the latter. Our experience does not substantiate this latter claim, nor is it clear that "toxic nodular goiter" is a different disease from "toxic diffuse goiter."

Thyroid suppression test—After a 12 month course of appropriately administered propylthiouracil, the thyroid suppression test is valuable in deciding whether or not a recurrence of hyperthyroidism is likely if treatment is stopped.[10] Administration of thyroid hormone to a person with normal thyroid function results in suppression of pituitary production of thyrotropin, and this is reflected by a fall in the 24 hour I^{131} uptake by the thyroid. This fall does not occur when thyroid hormone is given to a hyperthyroid patient, either because the hyperthyroid gland is functioning autonomously from the pituitary, or, as recent evidence suggests, because the pituitary or other organ elaborates an abnormal thyrotropin whose secretion is not subject to regulation by circulating thyroid hormone.[11-13] Treatment with propylthiouracil tends to restore the ability of thyroid hormone to suppress the I^{131} uptake, and it has been found that this phenomenon correlates with the prognosis for long-term remission.

The test consists of administering 3 gr. of thyroid U.S.P. a day for three weeks, during which time propylthiouracil treatment is continued. At the conclusion of three weeks, I^{131} uptake per 24 hours is measured. Patients with uptakes greater than 35 per cent in 24 hours are likely to have a recurrence of disease if propylthiouracil is stopped, and a longer course of treatment probably should be advised. An uptake of less than 35 per cent indicates that a recurrence is unlikely and treatment may be stopped at this point.

Special Instances of the Use of Antithyroid Drugs

Two circumstances in which antithyroid drugs are used deserve special mention: hyperthyroidism in children and adolescents and hyperthyroidism during pregnancy. In both situations we believe antithyroid drugs are clearly the treatment of choice. We have reservations regarding the use of radioiodine therapy in adults, and these reservations are even more forceful in youth and pregnancy. As well, there is considerable evidence indicating a relationship between ionizing radiation to the head and neck during childhood and the subsequent development of carcinoma of the thyroid.[14] Radioiodine treatment during pregnancy can be expected to destroy fetal as well as maternal thyroid tissue and, as with radiation of the pelvis in pregnancy, it carries a risk of inducing potentially malignant changes in the fetus. Surgical treatment has even less to recommend it in childhood than in adulthood and is a procedure to avoid during pregnancy because of its hazard to the mother and especially to the fetus. In both situations, antithyroid drugs can be used successfully.

In general, the use of propylthiouracil in juveniles is similar to that in adults. An initial dosage of 100 mg. three times a day is usual. The most important difference from the treatment of adult hyperthyroidism is that an even

longer duration of therapy is necessary for long-term remissions in young patients. Continuous treatment for two or three years produces results comparable to those obtained in adults who are treated for a year. In some instances, even longer treatment is indicated. Wilkins[15] described a patient whose symptoms were controlled with propylthiouracil for six and one-half years before there was a reduction in size of the gland, the prognostic importance of which has been mentioned.

Although all currently available modes of treatment of hyperthyroidism carry an increased risk for a fetus, the judicious use of antithyroid drugs in pregnancy can minimize this danger. Propylthiouracil and other antithyroid drugs cross the placental barrier and exert their effects on the fetal thyroid, producing goiter and hypothyroidism if used in too large amounts. A small goiter in an infant at birth is not a particular hazard and disappears rapidly. However, large goiters can lead to difficulty at the time of delivery due to impairment of neck flexion, and fetal deaths related to this factor have been reported. Consequently, during pregnancy it is wise to use amounts of propylthiouracil which just suppress thyroid function to normal or which permit a slightly hyperthyroid state to persist. After delivery, full suppression of the disease can be achieved and treatment continued in the usual fashion.

If the PBI level is used as a guide to the degree of thyroid function during pregnancy, allowance should be made for the fact that during the last trimester the PBI rises several micrograms per cent due to an increase in the thyroxin-binding capacity of plasma.[16] When used with this precaution, propylthiouracil permits a normal pregnancy to occur in the presence of hyperthyroidism with no undesirable effects on fetal thyroid function. It should be recalled that goitrogens pass into the mother's milk as well as across the placenta, and consequently breast feeding is contraindicated in a woman who is receiving antithyroid drugs.

Complications During Treatment

If treatment is begun with 300 to 400 mg. of propylthiouracil daily, and this amount of drug is continued, hypothyroidism frequently develops during the course of therapy. This complication often can be prevented by halving the dosage after two or three months of treatment. In cases in which hypothyroidism does develop, reducing the dose by half or more should suffice to restore the patient to a euthyroid level. A PBI determination is often helpful in deciding that a change in a patient's symptoms represents incipient hypothyroidism. A goiter which diminishes in size as a patient passes from hyperthyroidism to euthyroidism may enlarge again if hypothyroidism occurs. It should be emphasized that hypothyroidism which develops during the course of administration of antithyroid drugs is transient and disappears after cessation of treatment. In contrast to radioiodine, antithyroid drugs rarely cause permanent hypothyroidism.

Much of the hesitation in the use of propylthiouracil has arisen because of fear of toxic reactions, and much of this fear stems from confusion in regard to the occurrence of leukopenia and agranulocytosis. A review of 25 series of cases treated with propylthiouracil (a total of 2,491 patients) showed an incidence of toxic effects of 3.25 per cent.[17] The most common manifestations were leukopenia, agranulocytosis, skin rash, fever, urticaria, and arthralgia and myalgia. Uncommon reactions attributed to propylthiouracil included gastrointestinal disturbances, hair loss and pigmentation, vertigo, paresthesias and other neurologic symptoms, periarteritis and disturbances of the clotting mechanism. The majority of toxic reactions develop during the first two months of treatment, but a reaction may occur at any time while the drug is being administered.

We do not believe that leukopenia alone is an indication to modify treatment with antithyroid drugs. Leukopenia may arise in the course of hyperthyroidism and hence, at times, may be a reflection of the disease process rather than an effect of treatment. Leukopenia developing during treatment with propylthiouracil usually occurs without accompanying symptoms and subsides without incident. When agranulocytosis does appear, it does so

rapidly, with signs of infection. For these reasons we have not found it useful to perform routine leukocyte counts during treatment. Rather, we warn the patient to report immediately if he has fever, sore throat, severe respiratory infection, skin rash or other new symptoms.

The incidence of agranulocytosis in the 25 series of cases mentioned previously was less than 0.5 per cent, and in the 11 cases which arose there were no fatalities. If agranulocytosis or other significant toxic manifestation develops, treatment with propylthiouracil should be discontinued and either a different drug, such as methimazole, or radioiodine treatment should be substituted.

Factors in Choice of Method of Treatment

The ideal treatment for hyperthyroidism has yet to be discovered. Each of the three treatments currently used (surgery, radioiodine and antithyroid drugs) has its disadvantages. In selecting treatment, the physician and the patient must weigh the limitations of these various methods with respect to the individual concerned, and the method chosen should be the one which seems most advantageous for the particular patient. With two successful medical forms of treatment available, in our opinion, surgical treatment should play a very minor role in the management of hyperthyroidism. The results in terms of producing euthyroidism by subtotal thyroidectomy are no better than the results of medical forms of therapy, and in the best hands surgical treatment produces a significant incidence of hypoparathyroidism, recurrent laryngeal nerve paralysis, and postoperative morbidity and mortality, all complications which do not occur with medical treatment.

The objective in medical treatment is to produce a euthyroid patient, and in evaluating a form of treatment one must consider as unfavorable both recurrences of hyperthyroidism and, to a lesser degree, the development of permanent hypothyroidism. Treatment of hyperthyroidism with antithyroid drugs carries a high rate of recurrence, but if the foregoing plan of treatment is followed at least two-thirds of patients will become euthyroid for prolonged periods; and this fraction may be larger if longer periods of treatment are prescribed for patients in whom a thyroid suppression test fails to show suppression of the I^{131} uptake after 12 months of treatment.

Repeated doses of I^{131} can probably cure hyperthyroidism in all instances. After one dose of I^{131}, Cassidy and Astwood[18] found that 65 per cent of their patients became free from hyperthyroidism, and 89 per cent were cured after two doses. Despite elaborate formulas for the purpose, selection of a therapeutic dose of I^{131} is still largely a hit-or-miss affair, and high remission rates after a single administration of radioiodine are usually associated with a high incidence of post-treatment myxedema. In the study by Cassidy and Astwood, the incidence of permanent hypothyroidism after I^{131} treatment was 14 per cent. Although this complication can be treated easily and is generally not serious, ideally one wishes to avoid it. As previously mentioned, transient hypothyroidism occurs frequently during the course of treatment with antithyroid drugs but permanent myxedema occurs rarely if at all.

Propylthiouracil usually produces clinical improvement within two weeks after starting treatment, a more rapid response than with I^{131} therapy, which requires six weeks to three months for similar results. Antithyroid drugs frequently are prescribed in conjunction with radioiodine in order to produce rapid clinical improvement before the I^{131} takes effect.

Side effects of I^{131} treatment generally do not occur, although rarely a temporary exacerbation of hyperthyroidism may develop. A few deaths have been reported from this complication. The side effects of antithyroid drugs have been discussed previously. They are sufficiently serious to result in interruption of treatment in less than 2.5 per cent of cases.

The question of the induction of malignant changes with radioiodine is raised frequently in connection with its choice as a therapeutic agent. There is no evidence so far to indicate that patients treated with therapeutic doses of I^{131} have an increased incidence of malignant diseases or of any particular malignancy.

Nevertheless, other forms of ionizing radiation have required many years of use before their neoplastic potential could be evaluated, and time has increased our caution in using such agents. Therefore, radioiodine treatment may be regarded as carrying an unknown potential for inducing malignant changes. We believe it is wiser in young patients to avoid this risk and to accept the minor inconveniences of daily "pill taking" and long duration of antithyroid drug treatment.

The simplicity and cost of treatment are important, depending on the setting in which treatment is conducted and the resources of the patient. Antithyroid drug treatment can be carried out by the family physician without elaborate equipment, whereas I^{131} treatment requires the availability of and experience with radioactive materials and counting devices. Even for long-term treatment the cost of antithyroid drugs is considerably less than that of a single therapeutic dose of radioiodine. However, antithyroid drug therapy usually requires more office visits than does I^{131} treatment.

Summary

Twenty years of experience with antithyroid drugs have provided a background of information establishing the usefulness of these substances as therapeutic agents in hyperthyroidism. When used with due regard for the requirements of proper dosage, duration and distribution of administration, propylthiouracil and similar agents provide an effective, safe, inexpensive and convenient form of treatment. By interfering with the synthesis of thyroid hormone, propylthiouracil induces rapid remission of signs and symptoms. Permanent suppression of the disease occurs in the majority of patients treated for a year or more. Toxic effects, usually mild, occur in a small percentage of cases. Hyperthyroidism in youth and in pregnancy presents special problems, and in these circumstances antithyroid drugs are the treatment of choice. While both radioiodine and antithyroid drugs can be used successfully in adults, we believe that the uncertainty of the long-term effects of this form of ionizing radiation warrants the use of antithyroid drugs in most young adults with hyperthyroidism.

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Treatment of Chronic Diabetes Insipidus

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EDWARD C. CLARK

THE objective in the treatment of chronic diabetes insipidus is to control the distressing polyuria and polydipsia. Once these symptoms have been controlled, the treatment is still not completed until the physician has determined whether the diabetes insipidus is secondary to involvement of the hypothalamic-neurohypophyseal system by a disease that will respond to surgical intervention, irradiation or medication.

The polyuria and polydipsia are usually treated by hormonal replacement. The administration of chlorothiazide or related compounds and dietary restriction will also ameliorate these symptoms, but are less effective than hormonal replacement.

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Polyuria and polydipsia of diabetes insipidus are usually treated by hormonal replacement.

Posterior pituitary powder is the preparation of choice when it adequately controls the symptoms without side effects; when it does not, vasopressin tannate in oil should be used.

Once the symptoms are controlled, the physician should determine whether the diabetes insipidus is secondary to involvement of the hypothalamic-neurohypophyseal system by a disease that will respond to operation, irradiation or medication.

Hormonal Replacement

The polyuria and polydipsia of diabetes insipidus are the direct result of a decreased release of antidiuretic hormone by the posterior pituitary. The following preparations containing antidiuretic hormone are available for treatment of these symptoms.

Posterior pituitary powder U.S.P.—This is

available in bottles containing ⅛ oz. or in capsules containing ⅔ gr. of powder. The powder is placed on the nasal mucosa through which the active principle is absorbed. It is usually applied by sniffing pinches of powder from the finger tips or the back of the hand, much as one inhales snuff, or by blowing the powder into the nose with an insufflator consisting of a rubber bulb and a plastic chamber into which an open capsule of the powder is placed. Both methods frequently result in the powder's going beyond the nose into the rest of the respiratory tract and causing sneezing, coughing, wheezing or even asthmatic attacks. These undesirable effects can usually be avoided by rubbing the powder directly on the nasal mucosa with the tip of the little finger. If the patient has powder in the bulk form, it is placed on the finger tip by inserting the finger into the bottle. If the powder is in capsules, a capsule is opened and some of the powder poured onto the finger tip.

The antidiuretic effect of the powder lasts from three to eight hours. Patients are advised to use the powder at bedtime, during the night if needed, in the morning on arising, and once or twice during the day as needed. Each patient must determine for himself the amount of powder and the frequency with which it must be used for the most satisfactory results. A capsule of powder will usually last one to two days, depending on the severity of the diabetes insipidus.

Buccal tablets—Posterior pituitary powder can be compressed into tablets, which are inserted into the buccal pouch between the teeth of the lower jaw and the cheek. These tablets usually contain 100 mg. of powder and should not be sucked, chewed or swallowed, but allowed to disintegrate slowly in the buccal pouch so that the antidiuretic hormone can be absorbed through the buccal mucosa. They have a taste that is objectionable to some patients, take from 20 minutes to one hour to disintegrate, and have an antidiuretic effect lasting three to eight hours. Since patients need 2 to 4 tablets every 24 hours, it is obvious that this form of therapy is less economical than the application of powder to the nasal mucosa.

Aqueous vasopressin—Several aqueous preparations containing antidiuretic hormone are available. The one most commonly used is vasopressin (PITRESSIN®), which contains 20 pressor units per milliliter and comes in ampules of 0.5 and 1 ml. This preparation, when given in doses of 5 to 10 pressor units, has an antidiuretic effect lasting one to eight hours and can be given subcutaneously or intramuscularly. It can also be administered as an intranasal spray by means of an atomizer or by placing the solution on a small pledget of cotton, which is inserted into the nose or the vagina.

Obstetric posterior pituitary preparation (PITUITRIN®) also contains vasopressin and thus can be used to control diabetes insipidus. It is available in 0.5 and 1 ml. ampules containing 10 pressor units per milliliter or in 1 ml. ampules containing 20 pressor units, and is used in the same ways as the aqueous vasopressin.

Any of the aqueous agents may cause abdominal cramps, or angina pectoris in persons with coronary disease.

Vasopressin tannate in oil (Pitressin tannate in oil)—This preparation comes in ampules containing 5 pressor units in 1 ml. of peanut oil. It is administered intramuscularly, and whenever possible patients should be taught to give their own injections. Since the active ingredient is suspended in the peanut oil rather than being in solution, it is essential that the contents of the ampule be mixed thoroughly before injection. Warming the ampule to body temperature will facilitate withdrawal of the oily mixture. An intramuscular injection of 0.5 to 1 ml. provides relief from symptoms for 36 to 72 hours. The administration of doses larger than 1 ml. does not prolong the antidiuretic activity. Instead of taking the injections on a predetermined schedule, patients should be told to wait until the polyuria and polydipsia return before taking the next dose.

Treatment With Chlorothiazide

Chlorothiazide and related drugs will reduce the urinary volume of patients with diabetes insipidus by approximately 50 per cent.[1]

The mechanism of action is not known, but these compounds enable the kidneys to excrete a more concentrated urine. This effect is obtained by giving about 500 mg. of chlorothiazide twice a day, or comparable doses of related compounds.

Since these substances may cause potassium deficiency, agranulocytosis or other side effects, and since they are not as effective as antidiuretic hormone in reducing the urinary volume, they are not the preferred ones for treating diabetes insipidus. However, they are of definite value in decreasing the urinary volume of patients with nephrogenic diabetes insipidus, a condition that does not respond to the administration of antidiuretic hormone.[2]

Dietary Restriction

The solute load excreted by the kidneys determines in part the urinary volume in diabetes insipidus. Limiting the intake of protein and sodium chloride will reduce the solute load and in turn will reduce the urinary volume. Such measures are rarely needed when adequate hormonal replacement is used.

Treatment of Choice

The most effective treatment for the control of diabetes insipidus is the administration of antidiuretic hormone. Because of its ease of administration and relative inexpensiveness, posterior pituitary powder is the preparation of choice when it gives adequate control of the symptoms without producing side effects. Vasopressin tannate in oil should be used in patients whose disease is not adequately controlled or who have side effects from posterior pituitary powder. The long-term treatment of diabetes insipidus with aqueous preparations of vasopressin is totally unsatisfactory because of the cost and the frequent injections needed to obtain adequate control of symptoms.

It should be realized that although polyuria and polydipsia are annoying they are not harmful to the patient who can satisfy his need for water. On the other hand, if the patient is denied water or unable to drink, dehydration will occur and the administration of antidiuretic hormone and water will be lifesaving. In contrast, it should be realized that in a patient who is taking exogenous antidiuretic hormone, water toxicity may develop if water is given rapidly in large amounts. Under such circumstances the kidneys are unable to respond in a normal fashion by excreting large amounts of dilute urine in a short time. It is also for this reason that overtreatment with antidiuretic hormone should be avoided.

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SCIENTIFIC EXHIBIT

Diabetes Insipidus

Current Concepts in the Production of Antidiuretic Hormone

Clinical and Experimental Observations

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This exhibit was presented initially at the 1958 meeting of the American Medical Association in San Francisco.

Diabetes Insipidus

DIABETES insipidus is a clinical entity caused by a deficiency of the antidiuretic hormone of the posterior pituitary gland.

This entity is characterized chiefly by excessive thirst and the excretion of large volumes of dilute urine. The symptoms are relieved by the administration of antidiuretic hormone.

When diabetes insipidus is suspected clinically, the diagnosis can be confirmed by the series of tests illustrated on page 100.

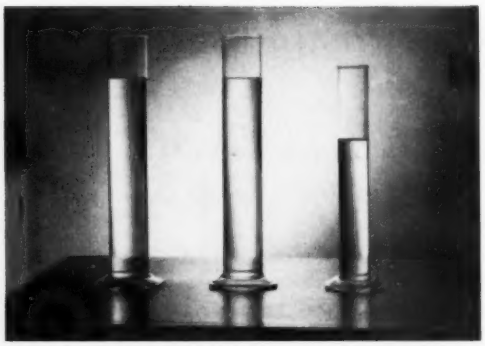
It should be realized that in many instances diabetes insipidus may be the manifestation of some underlying disease involving the neurohypophysis, as outlined in the classification of the causes of diabetes insipidus on page 99. Hence, it is essential to determine whether the condition is primary, that is, idiopathic or familial, or secondary to a tumor or some systemic disease. Differentiation may be made by the series of procedures shown on page 100. In some instances, however, it may be necessary to follow a patient for several years before the underlying disease can be diagnosed with certainty.

Classification of the Causes of Diabetes Insipidus

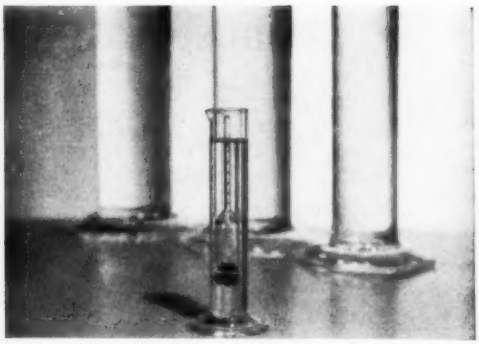
I. Primary diabetes insipidus
   A. Familial
   B. Idiopathic

II. Secondary diabetes insipidus
   A. Trauma
      1. Accidental
      2. Surgical
   B. Neoplasm
      1. Primary
         a. Pituitary adenoma
         b. Craniopharyngioma
         c. Meningioma
         d. Epidermoid
         e. Dermoid
         f. Teratoma
         g. Chordoma
         h. Pinealoma
         i. Optic glioma
         j. Giant-cell tumor of bone
      2. Metastatic
   C. Vascular disease
   D. Infectious disease
      1. Abscess
      2. Granulomatous infections
      3. Encephalitis
      4. Meningitis
   E. Systemic disease
      1. Sarcoidosis
      2. Xanthomatosis
      3. Leukemias, lymphomas and related diseases

The Diagnosis
of Diabetes Insipidus
May Be Confirmed



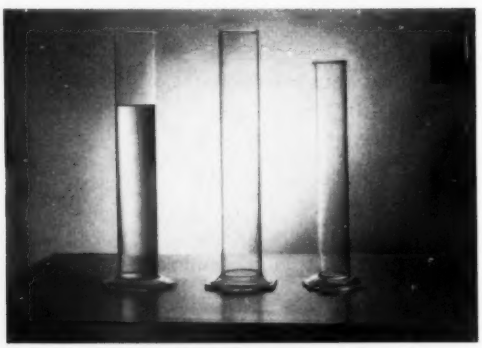
When the volume of urine excreted is consistently greater than 2500 ml. per 24 hours.



When, in the absence of renal disease, deprivation of water fails to evoke a concentrated urine.

When the intravenous administration of hypertonic saline solution fails to evoke a concentrated urine.

When the administration of nicotine fails to evoke a concentrated urine.



When the administration of posterior pituitary hormone results in a concentrated urine and a reduction in the urinary volume.

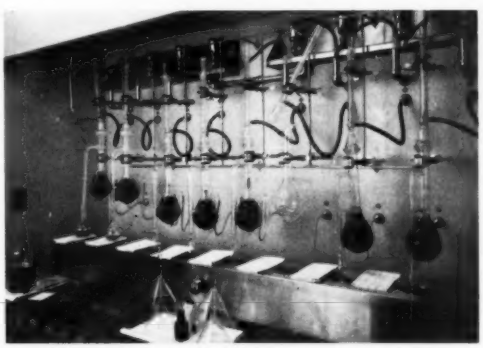
The Etiology
of Diabetes Insipidus
May Be Established

By reviewing the patient's family history for diabetes insipidus and by doing a general examination.

By studying the visual fields and by examining the fundus of the eyes.

By studying roentgenograms of the head for intracranial lesions.

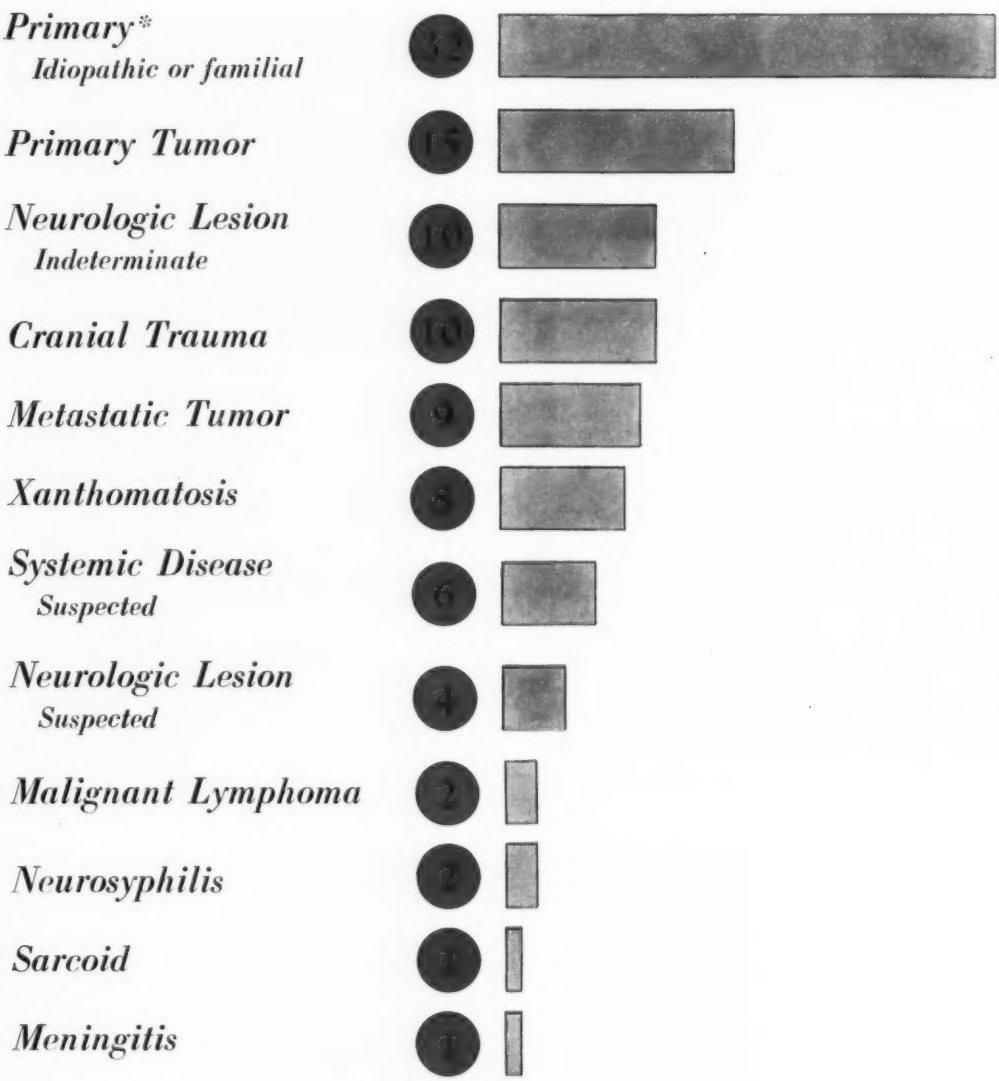
By doing a neurologic examination for clues to the presence of intracranial lesions.



By evaluating anterior pituitary function as a clue to the presence of intracranial lesions.

Etiology of Diabetes Insipidus

100 Cases Seen at the Mayo Clinic



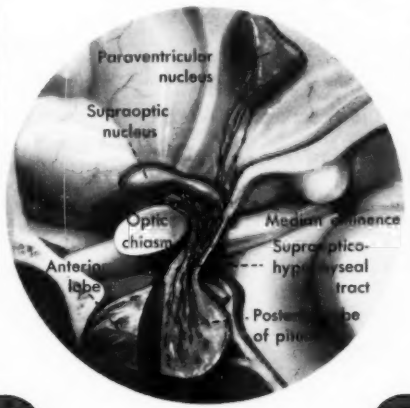
*In the absence of a familial history of diabetes insipidus, the diagnosis of "primary diabetes insipidus" must be made with caution. Diabetes insipidus may be the first symptom of a lesion involving the neurohypophysis and may precede by months or years other manifestations of the underlying disease.

Production and Action of Antidiuretic Hormone

According to current concepts, the antidiuretic hormone is produced in the supraoptic and paraventricular nuclei of the hypothalamus, migrates down the pituitary stalk and is stored in the posterior lobe of the pituitary. From there the hormone is carried by the blood stream to the renal tubules, where it helps to regulate the volume of urine.

When the Neurohypophyseal System Is Functioning Normally

An increase in the osmotic pressure of plasma results in release of antidiuretic hormone from the posterior pituitary into the blood stream. This effect is thought to be mediated through the hypothalamus.



When the Neurohypophyseal System Is Damaged by

Tumor, trauma or infection the formation or release of antidiuretic hormone is impaired and diabetes insipidus results. The defect in many cases of diabetes insipidus is not known.

Normally, about 180 l. of glomerular filtrate enters the proximal tubules in 24 hours.

Approximately 155 l. of the original 180 l. of glomerular filtrate is resorbed by the proximal tubules and about 25 l. passes on into the distal tubules.

Adequate antidiuretic hormone

Deficient antidiuretic hormone

In Normal Persons

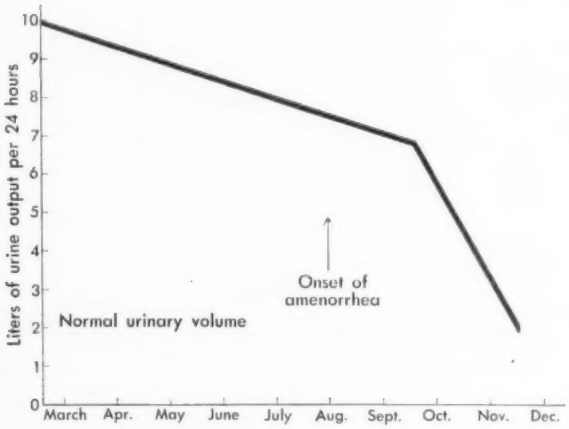
In the presence of normal amounts of antidiuretic hormone, most of the remaining 25 l. is resorbed in the distal tubules, leaving 1.5 to 2 l. to be excreted as urine. Hence, only about 1 per cent of the original 180 l. of glomerular filtrate leaves the body.

In Diabetes Insipidus

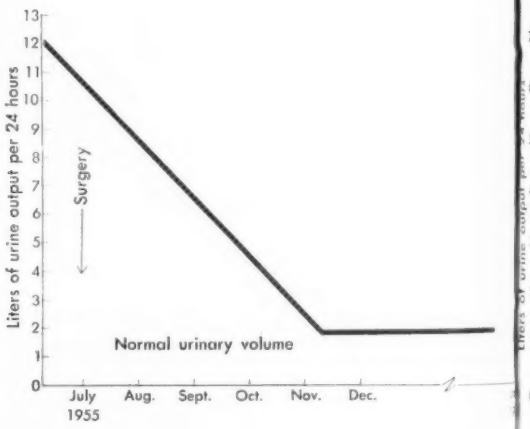
When antidiuretic hormone is absent or deficient, the resorption of fluid by the distal tubules is impaired and large amounts are excreted as dilute urine. The administration of antidiuretic hormone will correct this state.

Clinical Course of Diabetes Insipidus

1. Diabetes insipidus is not a fatal condition if the patient is not deprived of water.
2. The prognosis depends on the cause.
3. In uncomplicated primary diabetes insipidus, the urinary volume usually remains relatively constant for years.
4. The urinary volume will revert toward normal with the development of untreated anterior pituitary failure. See figure on left below.
5. The urinary volume may eventually revert to normal in posttraumatic or postsurgical cases of diabetes insipidus, even in the absence of anterior pituitary failure. See figure on right below.



Diabetes insipidus was the initial symptom in a 34 year old woman with a chromophobe adenoma of the pituitary. As the tumor grew, anterior pituitary failure developed and urinary volume decreased.

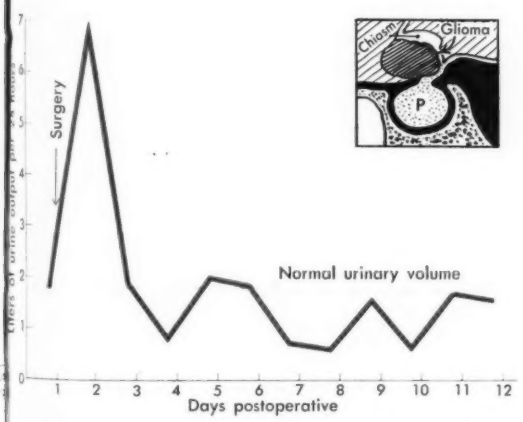


In a 16 year old boy with a craniopharyngioma, the urinary volume was normal. Postoperatively, diabetes insipidus developed only to subside later, despite treatment of concurrent anterior pituitary failure.

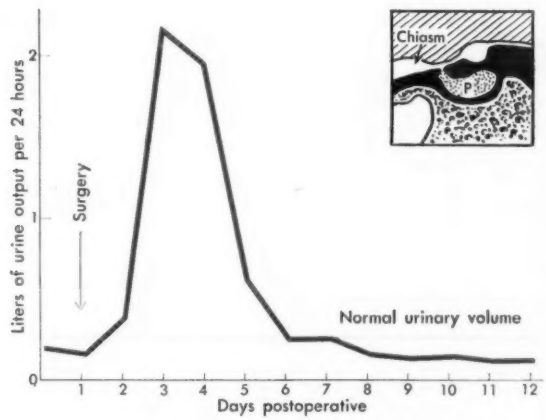
Patterns of Onset of Diabetes Insipidus

Temporary Pattern

When there is a limited injury to the neurohypophysis, temporary or transient diabetes insipidus may occur. Injury to the neurohypophysis is thought to result in failure of the posterior pituitary to release antidiuretic hormone into the blood stream. Within several days the neurohypophysis recovers from the injury, the function of the posterior pituitary is restored, antidiuretic hormone is released and the polyuria disappears.



Pattern of temporary diabetes insipidus in a human following surgical removal of an optic glioma. Insert shows diagrammatically the location of the tumor, the removal of which caused injury to the neurohypophyseal system.

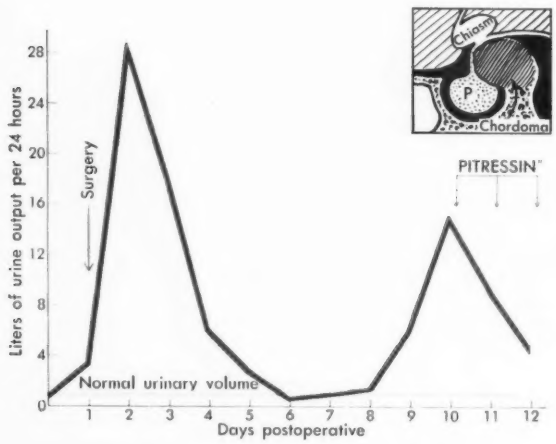


Temporary diabetes insipidus in a dog following partial section of the stalk of the pituitary. Insert, reconstructed from postmortem studies, illustrates the extent of the lesion in the stalk. Note that the pituitary and median eminence are intact.

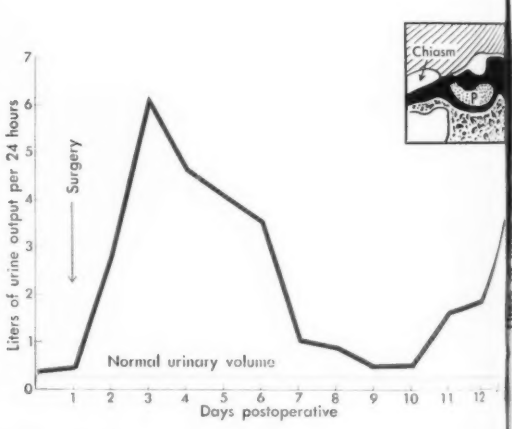
Triphasic Pattern

The classic triphasic pattern (transient polyuria, followed by apparently normal urinary output and finally permanent polyuria) follows destruction of the median eminence.

It is thought that denervation of the posterior pituitary inhibits release of antidiuretic hormone, causing immediate polyuria. After several days, the denervated posterior pituitary discharges antidiuretic hormone, producing an interphase of apparently normal urinary output. As the store of antidiuretic hormone is exhausted, permanent diabetes insipidus ensues.



Triphasic pattern in a human following surgical removal of a chordoma. Insert shows the location of the tumor.

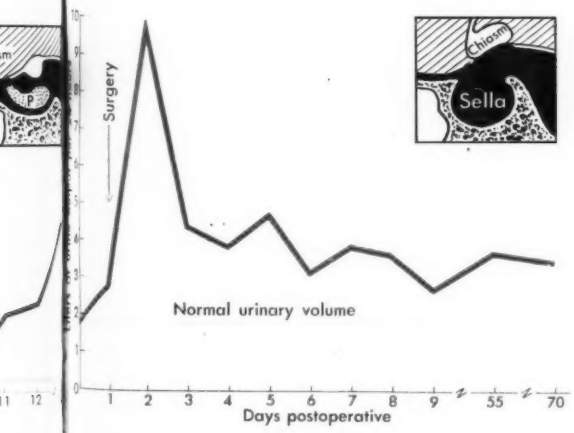


Triphasic pattern in a dog. Note in the insert that the pituitary was not removed and that the lesion involves the median eminence.

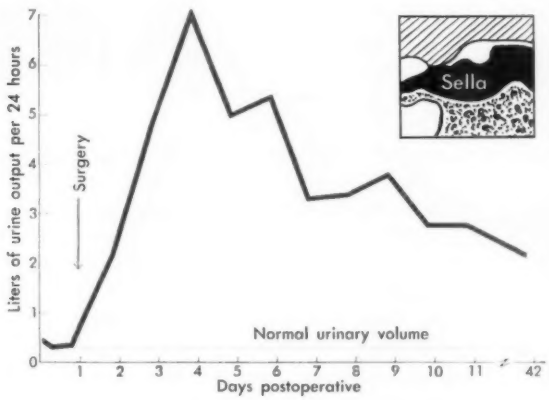
Permanent Pattern

Destruction of the median eminence of the neurohypophysis plus removal of the pituitary body and its stalk produces an immediate and permanent diabetes insipidus.

This pattern would be similar to the triphasic pattern except for the fact that the store of antidiuretic hormone in the posterior lobe of the pituitary and stalk is removed. Hence, immediate and permanent diabetes insipidus ensues without the intervention of an interphase.



Permanent diabetes insipidus in a human following hypophysectomy for disseminated carcinoma of the prostate. Insert, reconstructed from postmortem studies, shows that the pituitary and stalk were completely removed and that the median eminence was damaged.



Permanent diabetes insipidus in a dog following complete removal of the pituitary and stalk with destruction of the median eminence. Insert, reconstructed from postmortem studies, shows the extent of the lesion.

Water Fluoridation Is Feasible

WILLIAM T. INGRAM*

New York University, New York

Water Fluoridation Is Not New

WILLIAM T. INGRAM

THE practice of adding fluoride ion (F^-) to water is no longer new, nor is it experimental in many cities of the United States. Although cities such as Denver have had fluorides in the public water for years, the direct chemical addition of fluoride-bearing compounds to water was initiated in Grand Rapids, Michigan, in 1948. By 1959, over 36 million persons were being served with water containing fluoride ion in optimal dosage.

In 1957, I made an extensive study of the engineering practices employed in adding fluoride compounds to water. Research investigations were conducted by both correspondence and personal visits to 20 major cities with populations ranging from 135,000 to around 4.5 million. In each of these cities, fluoride-bearing compounds were added to the public water supply in controlled amounts. Five of the cities—Chicago, Philadelphia, Cleveland, Baltimore and Washington, D. C.—each serve over one million population and provide 34 per cent of the fluoridated water in the United States. Water systems of San Francisco, St. Louis, Milwaukee, Pittsburgh, Denver, Buffalo, Louisville, Indianapolis and Miami each serve 500,000 or more persons.

Figure 1 shows the population served in each of the 20 cities, and table 1 shows pertinent data on each city system. It will be observed that the average daily flow of water ranges from 19.8 million gallons per day (m.g.d.) to over 1000 m.g.d. and that the per capita consumption ranges from 107 gallons per capita per day (g.c.d.) to nearly 230 g.c.d. Miami obtains its entire supply from wells, and Denver obtains 18 per cent of its water from the ground. The other cities depend almost entirely on surface water sources.

Fluoridation in Complex Water Systems

In every city system, water is treated in some way before it reaches the distribution system. Table 2 shows the variation in treatment and the systems employing each type of treatment. All systems studied have chlorina-

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This discussion is based in part on material appearing in the report "Water fluoridation practices in major cities of the United States," prepared by the Research Division, College of Engineering, New York University for the New York State Department of Health, September 1958.

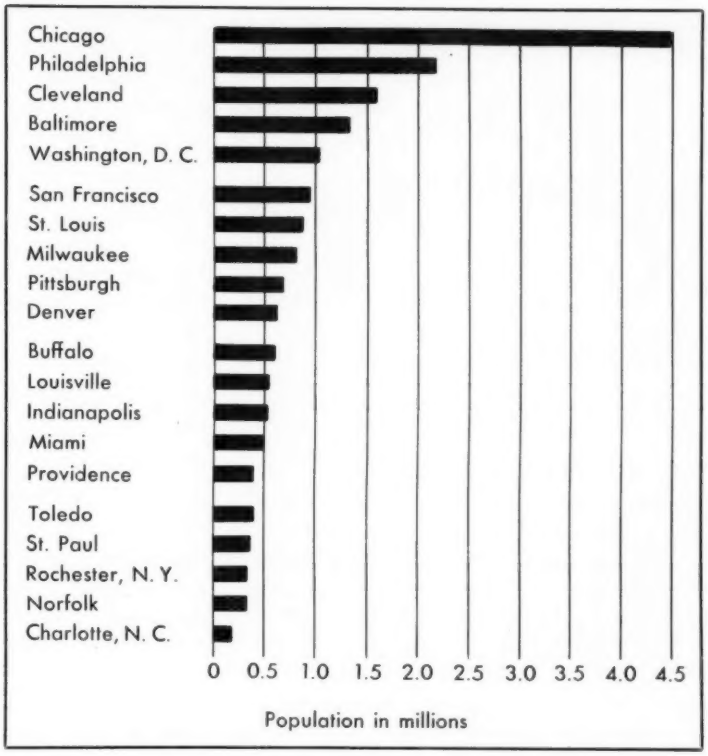

FIGURE 1. Population in 20 cities with fluoridated water service.

TABLE 1

DATA ON FLUORIDATION IN CITY WATER SYSTEMS

CITY	POPULATION SERVED FLUORIDATED WATER	FLUORIDATION STARTED	AVERAGE DAILY FLOW (M.G.D.)	ESTIMATED AVERAGE WATER USE (G.C.D.)
Chicago	4,488,000	May 1, 1956	1,031.5	229.8
Philadelphia	2,170,000	September 22, 1954	351.7	162.1
Cleveland	1,600,000	July 1, 1956	323.2	202.0
Baltimore	1,336,760	November 26, 1952	199.6	149.3
Washington, D. C.	1,044,000	June 23, 1952	160.0	153.3
San Francisco	941,100	August 1952	112.8	119.9
St. Louis	867,500	September 28, 1955	181.5	209.1
Milwaukee	812,700	July 22, 1953	140.4	172.7
Pittsburgh	675,000	December 20, 1952	105.0	155.6
Denver	641,000	June 4, 1954	105.2	164.1
Buffalo	600,000	May 1955	130.0	216.7
Louisville	550,000	August 1, 1951	82.0	149.1
Indianapolis	530,000	August 8, 1951	63.4	119.6
Miami	500,000	April 3, 1952	80.0	160.0
Providence	395,660	September 2, 1952	41.4	104.5
Toledo	390,000	December 31, 1955	68.0	162.6
St. Paul	357,000	October 2, 1952	40.0	112.0
Rochester, N. Y.	320,000	July 1952	42.0	131.3
Norfolk	317,500	August 12, 1952	41.3	129.9
Charlotte, N. C.	185,000	April 25, 1949	19.8	107.0
TOTAL	18,721,220			

TABLE 2

TREATMENT PLANTS IN CITY WATER SYSTEMS

TYPE OF TREATMENT	SYSTEMS (NUMBER)
Primary sedimentation	7
Chemical coagulation and sedimentation	19
Rapid sand filtration	18
Slow sand filtration	4
Softening	4
Corrosion control	11
Iron removal	1
Taste and odor control	12
Chlorination	20
Chlorination plus ammonia	8
Chlorine dioxide	4
Ozonization	1

tion; 19 have chemical coagulation and sedimentation, and 18 have rapid sand filtration. Washington, D. C., Pittsburgh, Denver and Philadelphia have slow sand filtration units in operation.

The pipelines required to transmit and distribute water in large city systems cover many miles. Chicago has more than 4000 miles; Philadelphia has nearly 3000 miles; Baltimore has more than 2000 miles; and several cities have 1000 or more miles of pipelines. Sizes of pipelines range from 6 to 93 in. in diameter. Materials of construction include cast iron, concrete-lined cast iron, concrete, steel, asbestos cement, lead and galvanized iron. Some cities have tunnels that are in rock or lined with concrete.

Transmission pipelines from treatment plants to distribution systems are sometimes quite long. Rochester, New York, has 35 miles; St. Louis, Denver and San Francisco have about 28 miles each. Several other cities have more than 10 miles of transmission pipelines to the storage reservoirs.

All cities have distribution reservoirs; some reservoirs are elevated tanks, and others are excavated in the ground. Capacities of such reservoirs range from one million gallons (elevated) to San Francisco's 2900 million gallons. Water may flow in and out of the reservoirs as water use varies during the day, week and season of the year. Actual water service may begin near a treatment plant or may be at the end of a long line of transmission and distribution into and out of one or more reservoirs. Thus, the flow time following fluoridation may be as little as two minutes (Indianapolis and Toledo) or as long as five days (Toledo and Washington, D. C.).

Temperature of water in distribution systems depends somewhat on the source, various characteristics of the system, operating schedules, and climate. In Miami, the average water temperature is 75° F., with little variation. In Baltimore, the temperature varies from 37 to 75° F., with an average of 54° F. In St. Paul, the temperature ranges from 35 to 79° F., with an average of 54° F.

Pipeline pressures in a system are extremely variable. Normal pressures are in the range of 40 to 60 lb. per square inch (p.s.i.). Pressures in the Pittsburgh system range from 25 to 235 p.s.i.; in St. Paul the range is from 5 to 95 p.s.i., and in Louisville it is from 40 to 150 p.s.i.

Water characteristics show a wide range of chemical and physical extremes. St. Louis, taking water from both the Missouri River and the Mississippi River, must treat highly turbid water. Miami must soften its clear ground water. Philadelphia must remove iron and manganese. The pH of waters ranges from 6.4 to 9.15. Fluoride ion was found in 17 waters on which mineral analyses were reported.

The foregoing description of characteristics of various water systems demonstrates a diversity of conditions related to source, treatment, temperature, pressure, chemical and physical properties of water, length of pipelines, piping materials, storage and operation. The one item common to all is the introduction of fluoride-bearing chemicals into a complex system at rates which provide optimal fluoride ion content in the water being supplied to the system.

Water Fluoridation as Part of Treatment Process

Waterworks engineers and managers of water utilities are accustomed to the problems of adding chemicals to water to produce a desired quality. Chemicals are added to soften hard water. The plant superintendent can predict what will happen to the water quality.

TABLE 3

FLUORIDATION CHEMICALS

CHARACTERISTICS	SODIUM FLUORIDE	SODIUM SILICOFLUORIDE	HYDROFLUOSILICIC ACID
Molecular weight	42	188.05	144.06
Solubility	4 per cent (at 60° F.)	0.4 per cent (average at 75° F.)	—
Form	Powder	Powder	Liquid
Purity (per cent)	95-98	98.5	30
Fluoride (per cent)	43-45	60	23.75
pH	6.5 (1 per cent solution)	3.5 (saturated solution)	—
Weight	65-90 lb. per cubic foot	72 lb. per cubic foot	10.5 lb. per gallon (2.49 lb. fluoride per gallon)
Pounds per part per million gallons of water flow	19.3	14	35.03 (3.34 gal.)

He uses equipment designed to weigh, mix and treat. He employs laboratory analyses to check his operation, and guided by such analyses he makes the adjustments that are required. The addition of fluoride-bearing chemical compounds and the control of dosage to maintain desired levels of fluoride ion actually are not unusual problems for one experienced in water plant operation.

Application of fluoride-bearing materials to water is accomplished essentially in the following steps:

1. Chemicals used include sodium fluoride (NaF), sodium silicofluoride (Na_2SiF_6) and hydrofluosilicic acid (H_2SiF_6).

2. Dry materials such as sodium fluoride and sodium silicofluoride are mixed into a solution. Liquids such as hydrofluosilicic acid are stored in feed tanks.

3. The solution containing fluoride ion is piped to a point where it can be added to water and is well mixed by some form of turbulent flow, as in a conduit, at a weir, or at a discharge well.

4. The mixed water flows to a storage basin or a transmission pipeline and is carried to the distribution system.

The point at which fluoride-bearing materials enter the system varies at different plants. For example, in Washington, D. C., fluoride ion is added in one system before coagulation; in Pittsburgh, the chemical is added to the influent in the sedimentation basins.

Chemicals must meet rigid specifications provided in the Standards of the American Water Works Association.[1-3]

The physical and chemical characteristics of fluoridation chemicals are shown in table 3. The solubility of the chemicals must be considered if it is desired that material be fed as a solution. To provide a dosage of 1 mg. per liter, 19.3 lb. of sodium fluoride is fed into 58 gal. of water and applied to one million gallons of water flow; 14 lb. of sodium silicofluoride can be fed into 355 gal. of water, which is then applied to one million gallons of water flow to provide a dosage of 1 mg. per liter. Acid is already in solution, and, when 23.75 per cent acid is applied at the rate of 35.03 lb. per million gallons, a dosage of 1 mg. per liter fluoride ion is obtained. Hence, an acid-feed mechanism applying 3.34 gal. of 23.75 per cent acid per million gallons is applying 1 mg. per liter of fluoride ion.

Control of Chemical Additions

Equipment for measuring and mixing the chemical is available from a number of manufacturers. Figures 2 through 4 show typical installations. In the 20 cities listed in figure 1, there are 37 fluoridation stations in which are located 46 feeder units. Chicago has three

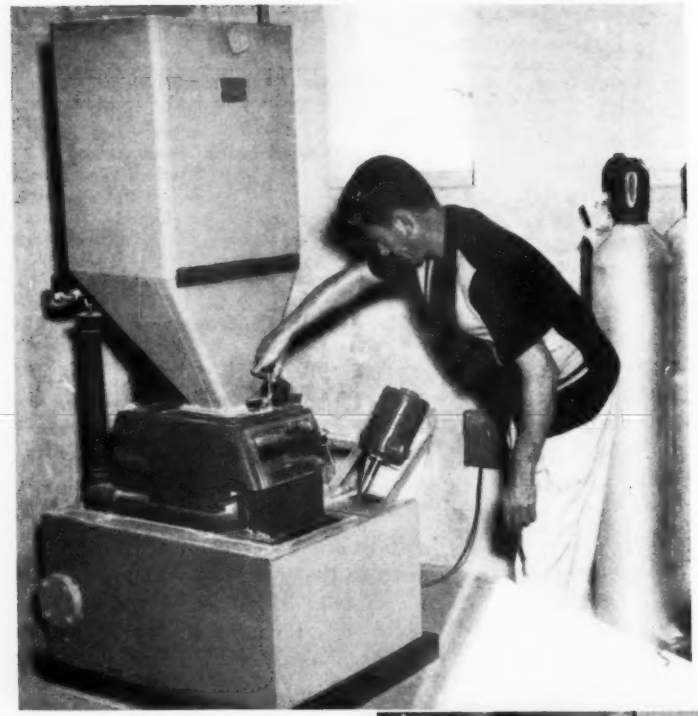

FIGURE 2. A volumetric fluoridation unit in Puerto Rico. This is a typical installation for a small filter plant.

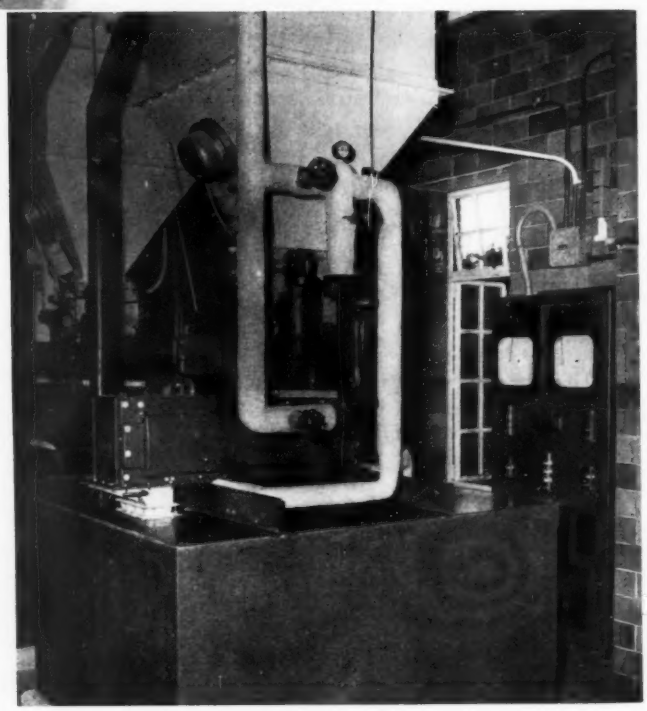

FIGURE 3. A gravimetric fluoridation unit in Washington, D. C., showing feeders, solution tanks, electric control panel and rotameter assembly.

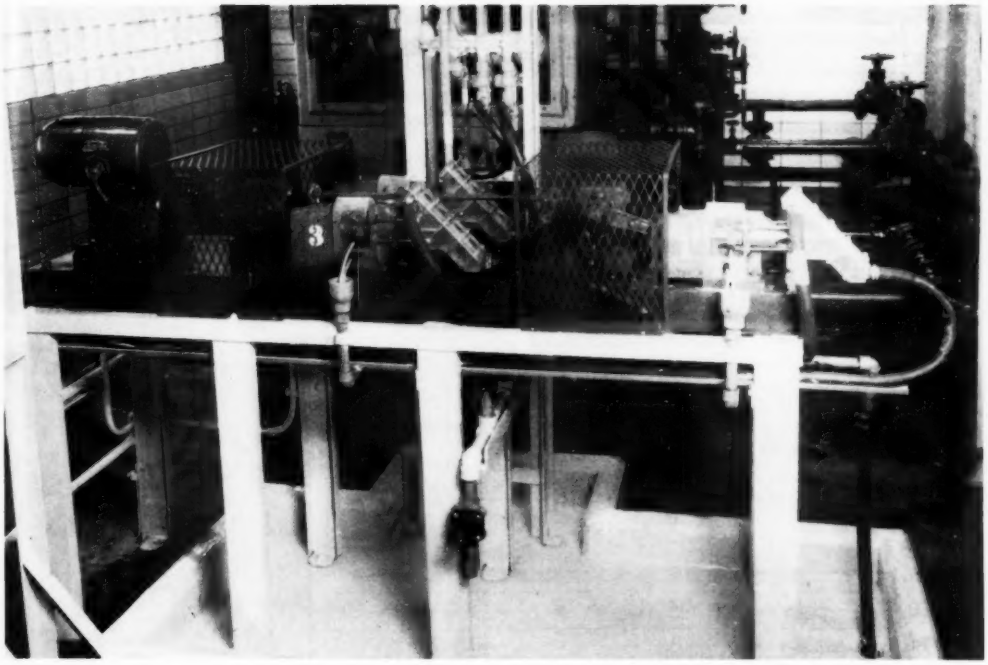

FIGURE 4. Proportioning pumps in the acid fluoridation installation at the South District Filtration Plant, Chicago.

stations with six feeders; Philadelphia has five stations with seven units, and San Francisco has three stations with four units.

In a fluoridation unit employing a weight beam and chemical feed regulator, the feed rate is set on a rotating disk by hand. The weight beam predetermines the load on a feeder belt fed through a lock-type device to keep the feed rate constant. Overloads sound an alarm, and on some machines an electronic control system stops the entire feeding mechanism if the weight belt is overloaded.

Figure 2 demonstrates a volumetric feeder. The machine is regulated by adjusting the area of the feeder orifice. Accuracy within 3 per cent is insured by weight check. This type of machine gives reliable service at small installations.

Another type of dry feeding unit is illustrated in figure 3. The chemical is fed from a hopper onto a belt which weighs the chemical. Mechanisms for controlling water volume and overload provide close regulation. Recording instruments show the amount of chemical fed. A clutch controlling a gate on the chemical feed is activated by a magnetic switch operated by deflections of the scale beam. Data show actual control within 0.3 per cent of the set rates.

Some volumetric feeders are equipped with a positive displacement feed screw adjusted by crank. Weight checks, feed rate and shutdowns are recorded on charts. Alarms and overload circuit breakers insure against overdosage.

Figure 4 shows a liquid feeder. The pumps are positive in action and cannot overfeed. Protection is provided to prevent flow of the chemical in event of breakdown. Since all liquid must pass through the pump, none will flow when the pump is shut off.

Residuals Can Be Maintained

Once the chemical is in the water system there is little change in the residual fluoride ion. A graphic illustration of the continuity

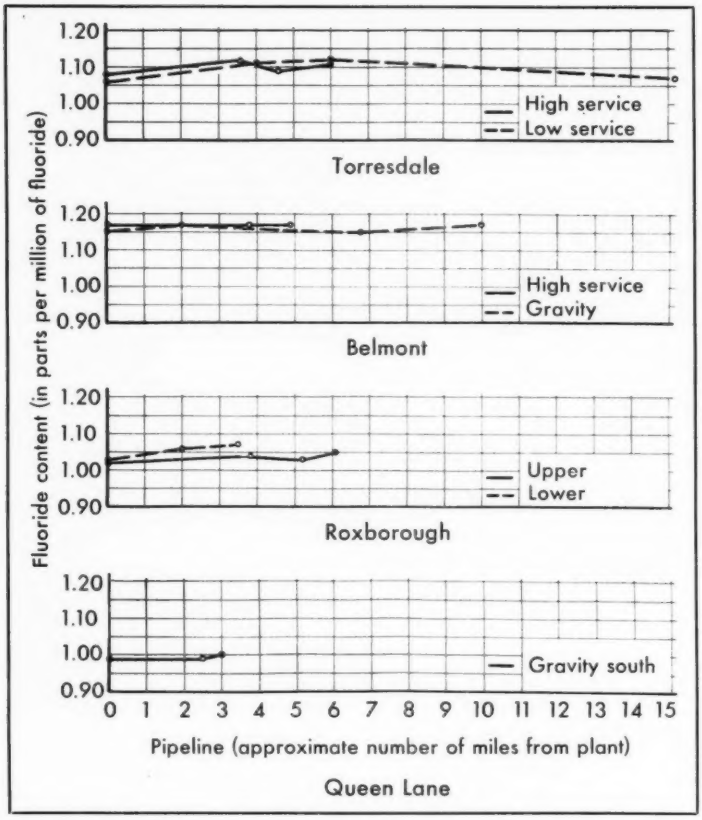

FIGURE 5. Fluorides in finished water in the Philadelphia water system from January through September 1957.

of the ion level is shown in figure 5. Even at distances up to 15 miles from the plant, residual fluoride ion persists. The change that is shown probably represents the daily variation in plant dosage and operating conditions in the system.

Another example is that in St. Louis, where results at one of the more distant points of two systems represented a flow time estimated at 56 hours. After 29 miles of traveling through pipelines and reservoirs, the average residual fluoride ion was the same as the average residuals at each of the plants.

At Denver, there are two systems, the Moffat supply and the South Platte supply. The latter contains natural fluoride, while fluorides are added to the Moffat supply. After some 20 miles of travel, the fluoride ion content in each system was as shown in the following.

FLUORIDE ION CONTENT
(Milligrams per liter)

	At plant	*At sampling point*
Moffat	0.7-1.2	0.7-1.2
South Platte	0.4-1.0	0.5-1.0

It is apparent from these examples that residual fluoride does not change significantly whether it is added at a treatment plant or is naturally present.

Costs of Fluoridation

Fluoridation of water is a relatively inexpensive means of providing protection to populations of cities. Figure 6 shows the cost per capita in 18 cities. The annual cost includes the amortization of construction and equipment to add fluorides to water, the cost of

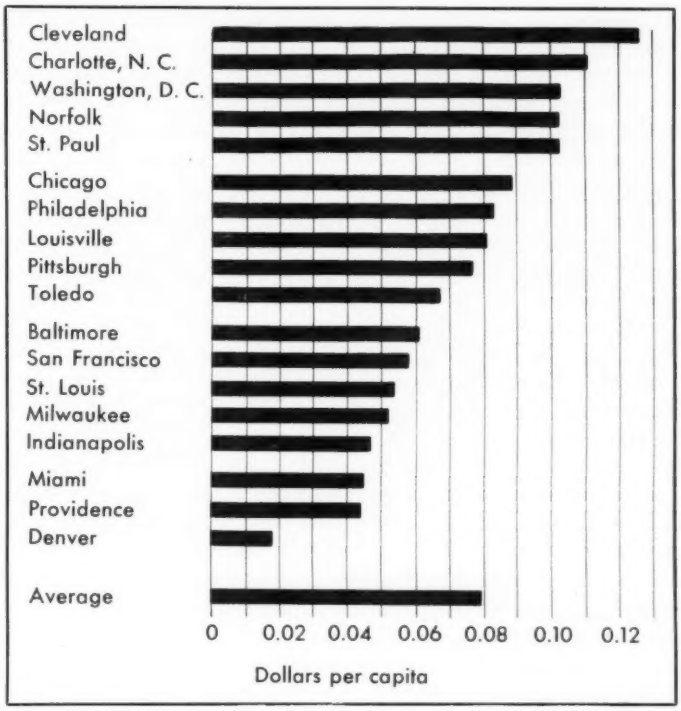

FIGURE 6. Cost per capita of fluoridation of water in 18 cities.

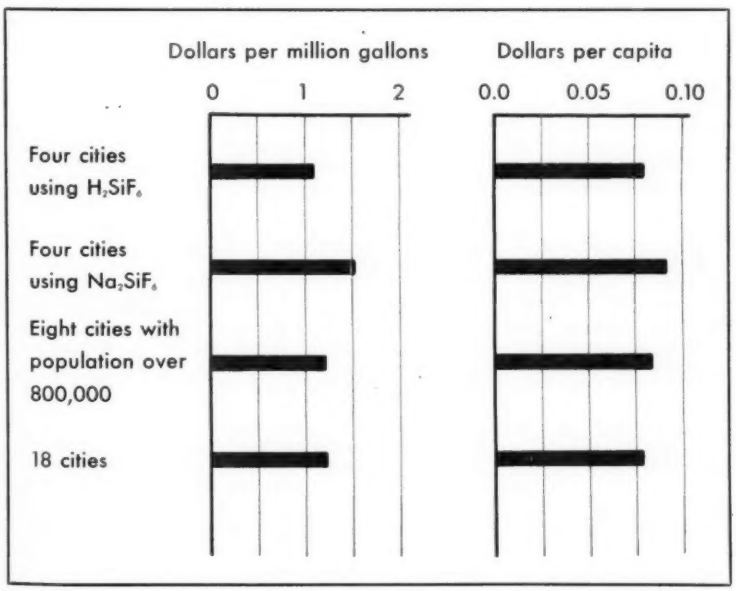

FIGURE 7. Unit costs of water fluoridation.

chemicals, and the cost of maintaining and operating the equipment. The cost ranged from 1.8 cents per capita in Denver, which has the advantage of naturally fluoridated water in part of its supply, to 11.2 cents per capita in Charlotte, North Carolina. The average cost for 18 cities was 7.9 cents per capita.

Costs of fluoridation vary according to the type of chemical used. Figure 7 compares four cities using acid, four cities using sodium silicofluoride, eight large cities, and 18 cities in the study. The annual cost with acid was 8.0 cents per capita, while the annual cost with silicofluoride was 9.2 cents per capita. Each of the eight supplies served populations of 800,000 or more, and the annual cost was 8.4 cents per capita, compared with 7.9 cents per capita for 18 cities. However, there is a difference among cities in per capita consumption of water, and the annual cost based on water use was $1.10 per million gallons for those using acid and $1.51 per million gallons for those using silicofluoride. The average cost of fluoridation among the eight large cities was $1.22 per million gallons; among the 18 cities, it was $1.23 per million gallons. It is to be noted that the amortization of construction and equipment is a rather insignificant part of the total charge, amounting to less than 0.5 cent per capita per year.

Eight of the large cities of the United States, with a total population of 13,260,000, are providing positive protection against dental decay at the modest cost of less than 34 cents per year per family of four. One needs only to price toothpaste for a cost comparison.

These studies have led to the conclusion that all engineering problems that occur in the handling of fluoride can be adequately solved and that the average city can well afford the costs of adding fluorides to water. It can be stated that the length of pipelines, the period of flow, and the materials to which water is exposed do not affect significantly the average fluoride content in a distribution system. Among the systems studied there has been no evidence of any pipeline corrosion traceable to the fluoride content of the water.

REFERENCES

1. AWWA Standard for Sodium Silicofluoride. AWWA B702-55. New York, American Water Works Association, 1955.
2. AWWA Standard for Fluosilicic Acid. AWWA B703-55. *Ibid.*[1]
3. AWWA Standard for Sodium Fluoride. AWWA B701-54. *Ibid.*,[1] 1954.

BOOKS RECEIVED

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-146; additional listings are on pages 123 and A-148.

Care of the Well Baby. Medical management of the child from birth to two years of age. By Kenneth S. Shepard, M.D., Director of Well Baby Clinics, Northwestern University School of Medicine, Chicago, with nine contributors. 224 pages with 31 illustrations. 1960, J. B. Lippincott Company, Philadelphia and Montreal. $3.25.

Modern Occupational Medicine. Edited by A. J. Fleming, M.D., Medical Director, C. A. D'Alonzo, M.D., Assistant Medical Director, Medical Division, and J. A. Zapp, Ph.D., Director, Haskell Laboratory for Toxicology and Industrial Medicine, E. I. Du Pont de Nemours & Company, with 22 contributors. Ed. 2. 586 pages with 66 illustrations and one color plate. 1960, Lea & Febiger, Philadelphia. $12.00.

Surgical Treatment of Unequal Extremities. American Lecture Series. By Charles Weer Goff, M.D., Associate Clinical Professor of Orthopaedic Surgery and Lecturer in Anatomy, Yale University School of Medicine, New Haven, Connecticut. 184 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $11.00.

Complications in Surgery and Their Management. Edited by Curtis P. Artz, M.D., Associate Professor of Surgery, and James D. Hardy, M.D., Professor and Chairman, Department of Surgery, University of Mississippi School of Medicine, Jackson, with 71 contributors. 1,075 pages, illustrated. 1960, W. B. Saunders Company, Philadelphia and London. $23.00.

Carcinoma in Situ of the Uterine Cervix. A study of 235 cases from the Free Hospital for Women. By Gilbert H. Friedell, M.D., Associate Pathologist, Massachusetts Memorial Hospitals, Arthur T. Hertig, M.D., Head, Department of Pathology, and Paul A. Younge, M.D., Assistant Clinical Professor of Gynecology, Harvard Medical School, Boston. 154 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $7.50.

CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Edited by William J. Donnelly, M.D., Chief, Section of Hematology

Case Report

A 27 YEAR old Negro laborer who previously had been in excellent health was admitted to Hines Veterans Administration Hospital on April 7, 1958, because of weakness in the left arm, left leg and back of five or six months' duration. Six months before admission, he noted "nervousness" (tremor) in his left forearm when holding objects in his hand. The weakness progressed and atrophy became apparent. He became unable to flex his thigh or to extend his knee easily. One month before he was admitted to the hospital, the weakness in his back increased until he was unable to get out of bed without assistance. It was necessary for him to roll on his side at the edge of the bed, drop his legs over the side, and pull himself up with his right arm.

The patient's history gave no evidence of syphilis or sensory or sphincter disturbances. He had had a brief bout of influenza in November 1957, about the time of the onset of his present illness. He drank five or six beers on week ends and smoked one and a half packages of cigarettes daily. In 1953 he lost a few teeth in an automobile accident. History was otherwise noncontributory, as were the family history and systemic review.

Examination revealed that the patient was chronically ill but mentally alert and cooperative. Temperature, blood pressure and pulse rate were normal. The general physical examination, including funduscopy, gave negative results. Cranial nerves were intact, with the exception of weakness and atrophy of the left trapezius muscle and fasciculations in the right side of the tongue. The abdomen was protuberant due to weakness of abdominal musculature. Full range of motion was present in all joints. There was severe muscular atrophy of the left shoulder girdle, arm, forearm, hand, gluteal region and anterior thigh. When supine, the patient could neither lift his left lower extremity nor sit up without help. The deep tendon reflexes were diminished, especially on the left side, and no pathologic reflexes were elicited. Heel-to-knee and finger-to-nose tests were performed poorly on the left side due to muscular weakness. The patient could stand, but he dragged his left leg when walking. The Romberg sign was negative, and all sensory modalities were intact.

Laboratory data—Results of serologic tests were negative. Hemoglobin was 15.7 gm. and the white blood cell count was 6000. Three urinalyses for porphyrins, as well as a complete urinalysis, gave negative results. Lumbar

puncture revealed the fluid to be clear, pressure 120, protein 55, sugar 86, and the gold curve 1111000000; serologic tests yielded negative results and bacterial culture was sterile. Nonprotein nitrogen was 33 mg. Fasting blood sugar was 108 mg. and carbon dioxide was 24 mEq. Total protein was 8.8 and albumin was 5.8. An electrocardiogram, an electroencephalogram, a chest x-ray and x-rays of the skull and spine gave normal findings.

Hospital course—While the patient was hospitalized, the strength of the initially involved muscles diminished to approximately 25 per cent of normal. He could not perform fine movements of the left hand. The proximal musculature appeared weaker than the distal musculature. Although weakness of the musculature of the right upper and lower extremities appeared, strength remained at least 50 per cent of normal. Deep tendon reflexes in the lower extremities appeared to diminish but could always be elicited; pathologic reflexes could never be elicited. Electrodiagnostic and electromyographic studies of the left tibialis anterior on May 26 revealed findings compatible with a lower motor neuron lesion; fasciculations were noted in the left pectoralis major. A foot-drop brace was supplied and the patient was given corrective and occupational therapy.

The patient started having productive cough and fever on July 16. His temperature was 103° F. rectally. A chest x-ray on July 17 revealed a shift of the mediastinum to the left and an elevation of the left hemidiaphragm, with atelectasis and possibly pneumonia of the left lower lobe. The white blood cell count was 25,000, with 88 neutrophils and 12 lymphocytes. Sputum culture yielded alpha streptococci and a *Klebsiella* species. Chest films on July 18 and 21 revealed pleural effusion on the left side and inflammatory infiltration and atelectasis of the left lower lobe. A large amount of purulent secretions was removed by therapeutic bronchoscopy on July 21. Following therapy with procaine penicillin G and sublingually administered ISUPREL® hydrochloride, the patient recovered quickly. On July 25, a chest film was normal except for a minimal pleural effusion on the left side.

Subsequently, the patient did well, although he was confined to a wheel chair for the remainder of his hospitalization because of progressive muscular weakness. On October 7, he was found unconscious and dyspneic. He was immediately placed in an Emerson respirator and given 1.0 cc. CORAMINE® intramuscularly. Although the pulse continued to be of good quality, spontaneous respirations consisted only of a few short gasps. A chest film made at bedside revealed no pulmonary pathologic condition. The patient did not regain consciousness and died 10 hours later.

Discussion

DR. S. HOWARD ARMSTRONG, JR. (professor of medicine, University of Illinois College of Medicine, Chicago): In this patient's history, the only questionable habit was that of smoking a package and a half of cigarettes a day for 17 years or so. His reported beer consumption on week ends was of a moderate degree. Except for the loss of a few teeth, there was no mention of any other injury to the head sustained in the automobile accident five years before he was admitted to Hines.

The motor disability which began in his left hand and became progressively worse occurred in the absence of certain symptoms. There were no convulsive or jacksonian manifestations, often seen when either an old subdural hematoma or a meningioma presses on the arm or hand area of the contralateral motor strip. There were no symptoms related to the vestibular system, and, although it was said that the patient dragged his left leg when walking, there was nothing to indicate trouble on the right side which might be related to a comparable lesion developing symmetrically. The development of this lesion was asymmetric. There were no convulsions, sensory disturbances or pain.

Examination of this man on admission showed that both abdominal and both cremasteric reflexes were absent. The absence of these reflexes is usually associated with pyramidal tract damage; however, there were no other findings on the more affected side (the left side) implicating specifically the pyrami-

dal tract. Although fine movements of the originally affected hand were impaired, the patient did not have a Hoffmann sign, a hand jerk, hyperactive deep tendon reflexes or spasticity. Signs usually associated with cerebellar lesions found on the left side were considered attributable only to weakness. His eyegrounds were entirely normal. Fasciculations in the tongue on the contralateral (right) side, with the other difficulties chiefly on the left side of the body, and some trapezius atrophy on the left side were the only symptoms which could have been due to a cranial lesion.

Now we must try to find a single localization for this lesion. It is possible that a condition may involve the motor strip of the cortex and progress from arm to leg or vice versa; however, the tongue and leg areas are at opposite ends of the cortical motor strip, and we therefore must drop temporarily the consideration of the cortex as the site of a single lesion. If we consider the pyramidal tract as it comes down through the corpus striatum, is gathered together in the cerebral peduncles, and is brought through its partial decussation, we still have no single explanation for the findings in this case. Even though the eleventh motor nucleus is at about the same level as the hypoglossal nucleus, it would be very difficult to explain fasciculations on the contralateral side of the tongue if all the troubles on this side were on the basis of the pyramidal tract. It is particularly important that no bladder or rectal disturbances were noted in this patient. The reported absence of Babinski's sign is not helpful; its presence would have been of great value in diagnosis.

Laboratory examinations showed that the patient had no porphyrinuria; pressure of the cerebrospinal fluid was normal, and the colloidal gold curve was well behaved. Total spinal fluid protein was somewhat elevated. Serum albumin was considerably elevated; this occurs spontaneously only during the recovery stage of hepatitis, or it may be produced by the injection of serum albumin. I think that on the day that this test was made the laboratory simply had a little extra protein in the distilled water.

The physiologic studies take us further from the pyramidal tract. Fasciculations were noted in the pectoral musculature; these were of the type indicative of either a nuclear lesion of an anterior horn cell or a lesion anywhere along the course of the motor root fibers. Such fasciculations can come from tumors, from syringomyelia, from cervical arthritis (seen in polo players), or from any number of lesions. However, in this patient, there was electromyographic evidence of fasciculations in the tibialis anterior and shoulder girdle on one side, and on the contralateral side such evidence was in his tongue. These are widely divergent locations in the nervous system. The uppermost location is the level of the nucleus of the hypoglossal nerve; the lowermost is down just about as far as you can get in the feet. It was noticed during this patient's hospitalization that the motor strength of the right extremities declined to about 50 per cent of normal. Thus, the same type of problem had begun in his right side.

A classical neurologist brought up in the school of Dejerine and Charcot would say that this was a highly atypical course for amyotrophic lateral sclerosis. Usually, the onset of amyotrophic lateral sclerosis is bilateral and symmetric. Variants of this condition include Erb's disease, in which a spastic element is predominant; Spiller's syndrome, which has a unilateral origin in the trunk and in the leg; Erb's palsy; Duchenne-Aran muscular atrophy; and Charcot-Marie-Tooth disease. Every variant has been described, including one limited entirely to the extrinsic musculature of the eye, with the nuclear lesion in the superior colliculi. In trying to determine which condition was present in this patient, the most important consideration is the course of his illness. He did well until about three months after his admission to the hospital, when an acute pneumonia developed in the left lower lobe. The diaphragm was elevated on that side; it did not move well, and therapeutic bronchoscopy showed that bronchial secretions were extremely thick. Were these bronchial secretions?

Nothing is mentioned in the protocol concerning further involvement of his tongue, of his muscles of deglutition, or of his speech,

particularly syllabic speech. An early sign in classic amyotrophic lateral sclerosis is loss of syllabic clarity of speech under the influence of one or two Martinis. After consuming moderate amounts of alcohol, the patient begins to "shush" a little more than he would have done under the same circumstances before the disease developed. This slowly progresses, usually over a period of a year. First, the labial sounds are lost; then the dental sounds and subsequently the lingual sounds are lost. Finally, speech is entirely laryngeal. At this time, the patient usually has a great deal of trouble swallowing; his tongue is not able to push food back into the grip of the pharyngeal muscles around the palate. He puts things in his nose or down his windpipe. At the time that this patient had aspiration pneumonia, did he have any trouble with the glossopharyngeal and the vagus nerves? Was anything known of his speech at this time?

DR. DONNELLY: No.

DR. ARMSTRONG: Such symptoms are particularly relevant because of the purulent secretions removed by the bronchoscope. If patients with amyotrophic lateral sclerosis have involvement of the inferior and superior salivary nuclei, the saliva has an extraordinarily high content of a highly viscous mucous material. This material looks like purulent sputum. It can be a problem clinically, because it impedes the already poor movements of the tongue and the muscles of deglutition. It gets food into such a mess that part of it goes down and part remains in the mouth. The part that goes down may be in the trachea, not in the esophagus. This could account for this patient's large amount of bronchial secretions in July, as well as for the pneumonia in the left lower lobe.

Dr. Littman, I do not know anything about those factors, either sympathetic or parasympathetic, that control the amount of glycoprotein in saliva. Can you tell us about them?

DR. ARMAND LITTMAN (chief, medical service): A thick, mucoid saliva, high in protein, is produced by sympathetic stimulation in the experimental animal, but I do not know of any lesion of the nervous system that might do this. It should be remembered that the presence of foreign material in the mouth is a potent stimulus to secretion of saliva, and you have made the point that these patients cannot clear away the material that remains after eating. In addition, such patients cannot swallow their basal salivary secretions automatically, and they drool.

DR. ARMSTRONG: We must then assume that there is a possibility that this patient had trouble up as high as the substantia gelatinosa Rolandi and the seventh nerve nucleus, from which come the fibers of the chorda tympani. The actual pathologic condition often is more extensive than the symptoms during life in this group of diseases that are related to amyotrophic lateral sclerosis. The involved cells often go all the way from Betz's cells of the cortex, through most of the motor nuclei, right on down to the end of the cauda equina. Yet, the neurologist frequently has been unable to pick up signs related to some of the lesions. Sexual difficulties, particularly impotence, often are present. Lesions in the nuclei of the thalamus also may produce mood changes, which curiously enough, in view of the rather hopeless prognosis, are more in the area of euphoria than of depression. Thus, if I am going to stick to a diagnosis of the Spiller variant of amyotrophic lateral sclerosis, I cannot predict to the pathologist the range of levels of the brain and spinal cord where this type of lesion may exist.

The pathologist's problem is, of course, to be sure that this is not another type of condition. Is there any kind of disseminated tumor or granuloma that can produce a syndrome of this type? We recently had a patient in Cook County Hospital who had a fungous disease of that extent, but we were never able to recover the fungus or get complement fixation. It turned out to be a perfectly standard *Torula* with many areas involved. However, the patient we are discussing was not that generally sick, and there was not enough involvement of other centers to indicate a syndrome of this type.

Let us consider the latter part of this patient's course. After he recovered from pneumonia, he lived from July to October. Then he was found in sudden respiratory distress

from which, despite the use of an Emerson respirator and other therapy, he did not recover. It is true that in the course of amyotrophic lateral sclerosis either unilateral or bilateral diaphragmatic paralysis can occur. However, if this were the case, the patient should have had more dyspnea before the final episode. It might have been another atelectasis or a pulmonary embolism. There is also one other possibility. This patient smoked one and a half packages of cigarettes for perhaps 17 years. He was a little young for carcinoma of the lung; however, the British have described in patients with carcinoma of the lung generalized central nervous effects which sometimes could mimic cerebellar disease, sometimes the Guillain-Barré syndrome. I recently saw a steel worker who had a perfectly classic Spiller variant of amyotrophic lateral sclerosis, with trunk weakness and unilateral fasciculations. At autopsy it was found that he had a carcinoma of the lung, which we did not detect on chest x-ray during life although a scalene node biopsy had shown carcinoma. I do not think anyone knows why this peculiar mimicking of degenerative diseases of the central nervous system is associated with carcinoma of the lung. In two of the British cases, it was associated with carcinomas other than of the lung. In some instances, neurologic symptoms have become evident before the symptoms or signs of a carcinoma of the lung. Going out on the furthest possible limb, I would say that this patient may have had an occult carcinoma of some type, associated with the Spiller variant of Charcot's syndrome.

DR. VICTOR JABLOKOW (assistant pathologist, laboratory service): Dr. Miree, are you ready to comment on the x-rays?

DR. JAMES MIREE (staff physician, radiology service): A film of the cervical spine did not show any pathologic condition or platybasia. The chest x-ray made on admission gave strictly negative findings, while the x-ray on July 17 showed a shift of the mediastinum to the left, with a small amount of fluid and a little infiltration in the left lower lung field. The marked shift is consistent with atelectasis. There also was elevation of the left hemidiaphragm. The atelectasis continued over several days; the diaphragm became more elevated and the infiltration became more intense. On July 21 there was more infiltration of the left lung; the right lung was still clear, and there was still a shift of lung structures to the left, all indicating atelectasis of the left lower lobe. On July 23, the process was clearing, but there was still a little residual density behind the heart, some atelectasis, and elevation of the left half of the diaphragm. On July 25, the chest was practically back to normal. The left hemidiaphragm was still slightly elevated and a suggestion of minimal infiltration behind the heart was still present. The last chest film of this patient was made on October 7 with a portable machine. It showed nothing but diffused lung markings due to rapid breathing; the heart and mediastinal structures were in normal position, and the trachea was in the midline.

DR. JOHN R. FINKLE (staff physician, spinal cord injury service): This seems to be a case of amyotrophic lateral sclerosis. The fact that no pathologic reflexes were found does not mean that they were never present. Surely at some time there must have been a Babinski sign. The deep tendon reflexes are generally hyperactive in early amyotrophic lateral sclerosis, and later they may become diminished or absent. We would not find this with a progressive muscular atrophy or with a dystrophy.

DR. JABLOKOW: This man showed marked atrophy of the left side of the body, involving the left arm, shoulder girdle, pectoralis muscle and lower extremity, including the gluteal region.

The combined weight of the lungs was 1400 gm.; they were so edematous that a large amount of frothy fluid exuded from the cut surfaces without pressure. Grossly, they showed fine granularity around the bronchi; histologically, they showed acute bronchitis and severe pulmonary edema. There were numerous areas of hemosiderin-filled macrophages in the alveoli, indicative of chronic pulmonary congestion. No aspirated material was found at autopsy.

The brain weighed 1,650 gm. and grossly appeared edematous. There were such severe

FIGURE 1. Myelin stain of section of spinal cord showing degeneration (pale areas) of lateral pyramidal tracts.

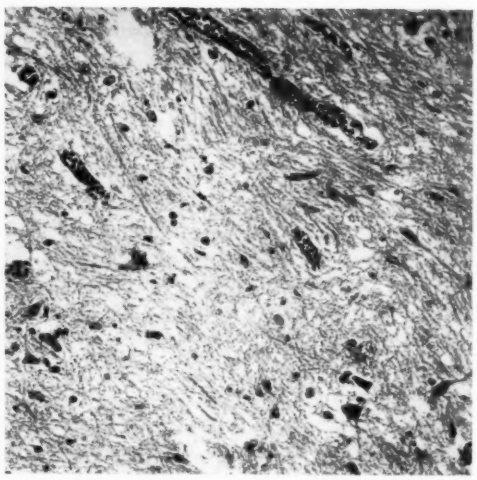

FIGURE 2. Hematoxylin-eosin stain of anterior horn of section of spinal cord revealing loss of nerve cells, rarefaction and gliosis.

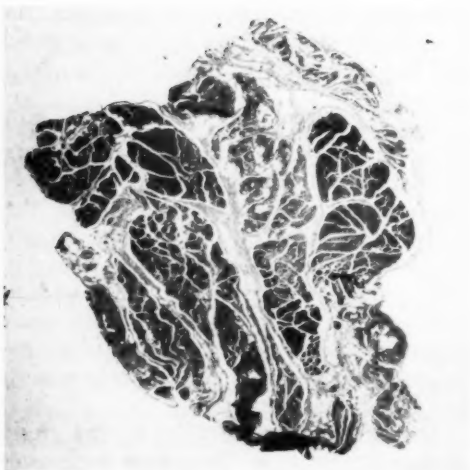

FIGURE 3. Section of leg muscle showing marked atrophy of some muscle fibers with increase in adipose tissue.

congestive changes present in the meninges that on gross examination there appeared to be multiple focal subarachnoid collections of blood. There was severe dilatation of the vessels in both the white and the gray matter, but there was no hemorrhage or tumor.

The diagnosis, as Dr. Armstrong ascertained, was amyotrophic lateral sclerosis. This disease was first described very thoroughly by Charcot in 1881; subsequent investigators have added little to his description. The pathologic findings in this disease consist of degeneration of anterior horn cells in the spinal cord, of the motor nuclei of the brain stem, and of the giant pyramidal cells in the cortex, with secondary degeneration of the corticospinal and corticobulbar tracts and with muscle atrophy secondary to these degenerative changes. When microsections of the spinal cord at many levels were stained for myelin, they showed loss of myelin in the lateral corticospinal tracts bilaterally (figure 1). The changes were most pronounced in the upper portion of the spinal cord. Multiple sections at various levels of the spinal cord showed marked loss of the ganglion cells of the anterior horns. There were mild gliosis and rarefaction of the anterior horns (figure 2). Sections at different levels of the spinal cord showed the presence of a large amount of lipochromic pigment, more than would be expected in a patient of this age.

The muscles of the leg also showed marked changes. In amyotrophic lateral sclerosis, the degeneration of the anterior horns and the upper motor neuron usually progresses slowly and does not involve all the cells at the same time. The nuclei are involved consecutively, so that we see atrophic changes in some of the muscle bundles while others are still intact. Microsections of the leg muscle in this patient showed marked atrophy with fat infiltration. In the same longitudinal section of muscle, there was normal muscular structure in one area, while in another the muscles were atrophic, with some increase in fibrous tissue (figure 3). Little or no inflammatory changes were seen in the muscular tissue. There was some increase in fibrous tissue, but no active proliferation of fibroblasts. The corticospinal tract and anterior horn cells showed marked degenerative changes, with severe secondary muscular atrophy. These findings are those of amyotrophic lateral sclerosis.

Books Received

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-146; additional listings are on pages 116 and A-148.

Hypnosis in Skin and Allergic Diseases. By Michael J. Scott, M.D., Instructor in Medicine, University of Washington School of Medicine, Seattle. 161 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $6.50.

Aids to Gynaecology. By W. R. Winterton, F.R.C.S., Obstetric and Gynaecological Surgeon, Middlesex Hospital, London. Ed. 12. 214 pages, illustrated. 1960, Baillière, Tindall and Cox, London. Distributed by The Williams & Wilkins Company, Baltimore. $3.00.

Dietary Proteins in Health and Disease. American Lecture Series. By James B. Allison, Ph.D., Director, and William H. Fitzpatrick, Ph.D., Honorary Associate Research Specialist, Bureau of Biological Research, Rutgers University, New Brunswick, New Jersey. 86 pages. 1960, Charles C Thomas, Springfield, Illinois. $4.50.

The Year Book of Pediatrics (1960-1961). Edited by Sydney S. Gellis, M.D., Professor and Chairman, Department of Pediatrics, Boston University School of Medicine, Boston. 479 pages, illustrated. 1960, The Year Book Publishers, Inc., Chicago. $8.00.

Obstetrical and Gynaecological Pathology. For postgraduate students. By R. E. Rewell, M.D., Consultant Pathologist, The Women's Hospital, Liverpool, England. 435 pages, illustrated. 1960, E. & S. Livingstone Ltd., Edinburgh and London. Distributed by The Williams & Wilkins Company, Baltimore. $10.00.

The Chemistry of Thyroid Diseases. American Lecture Series. By Rosalind Pitt-Rivers, Ph.D., and Jamshed R. Tata, D.Sc., National Institute for Medical Research, Mill Hill, London. 83 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $4.50.

Fundamentals of Chest Roentgenology. By Benjamin Felson, M.D., Professor and Director, Department of Radiology, University of Cincinnati College of Medicine, Cincinnati. 301 pages with 450 illustrations. 1960, W. B. Saunders Company, Philadelphia and London. $10.00.

Self-help Devices:

Selection of Wheel Chairs

General Considerations

EDWARD W. LOWMAN AND HOWARD A. RUSK

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THIS article is concerned with the prescription of a wheel chair for the patient for whom the chair will become a way of life. If the illness has not reached a plateau, final purchase of a chair should be deferred until the physician is reasonably sure of the degree of permanent incapacity. In this interim, it is best to rent a wheel chair from a reliable hospital supply house, where credit is often given toward the final purchase of a chair.

The prescription for a wheel chair should provide for the patient maximal comfort, safety, maneuverability and independence.

Maximal Comfort

Maximal comfort entails having a wheel chair that "fits." A patient who is 6 ft. tall or over may need an oversized, specially prescribed chair, with attention given to the length of the patient's legs and trunk, since a seat of special depth or with a raised back may be indicated.

A heavy-duty chair should be ordered for the patient whose weight exceeds 175 lb. Points of greatest strain should be reinforced. Measurements should always be taken while the patient is seated, with braces, seat cushion or seat board included, if these are used. If the braces are not available, an extra 1½ in. should be allowed to accommodate them.

A full-reclining or semireclining back adds considerable comfort for the patient who cannot sit up straight, e.g., those with severe deformity of the hip joints or involvement of the spine. These chairs are always equipped with footrests that are adjustable in length and height. The footrests should also be removable to permit closer proximity to working levels and transfer.

*Supported at the Institute by the Arthritis and Rheumatism Foundation.

Standard chairs are fitted with a reinforced canvas sling-type seat. Because of pressure areas, many patients will need supplementary cushioning. Others may find it more comfortable to sit on a hard seat, provided there is no contra-indication. When a hard seat is indicated, it should be removable so that it will not interfere with collapsing the chair for transportation and storage.

Maximal Safety

For maximal safety, the chair must be in good alignment. It is the responsibility of the patient or the person caring for him to keep the chair in good working condition to prevent corrosion and malfunction. All chairs should be fitted with brakes which are within easy reach and have removable extension handles, if necessary. The 8 in. casters insure greater maneuverability and stability than the 5 in. In cases of spasticity of the lower extremities, the chair should be equipped with toe or heel loops or both to control overflow motions. Straps across the thighs are occasionally necessary.

Maximal Maneuverability

Maneuverability of the chair in both the home and the place of work must be considered. Doorways and hallways must be measured to make certain that the patient can pass through them and reach all areas. There must also be sufficient room for him to turn the wheel chair in the rooms that he will be using. In private homes, it is usually possible to adjust the home to fit the chair, but in today's smaller apartments this problem may not be so easily solved.

Maximal Independence

The chair should afford the patient maximal independence in performing the activities of daily living. Transfer to and from the chair and approach of the chair to working levels form the basis for such activities. The problem is to bridge the gap between the chair and other furniture and equipment. Several factors in the construction of wheel chairs must be considered.

Detachable arms are preferred to stationary arms because they permit closer proximity to working surfaces and expedite transfer sideways (figures 1 to 5).

Removable or swing-out footrests or legrests also permit closer approach and expedite transfer forward (figures 6a and b).

A removable back, preferably with snaps (figure 7), permits transfer backward.

The hydraulic elevating seat (figure 8) is helpful to patients who have difficulty sitting down to or standing up from the standard-height wheel chair, who cannot transfer because of differences in height between the wheel chair and other areas (figure 9), and who must reach and work at various levels (figure 10).

The patient shown in figure 10 is sitting too low. Ideally, the work level should be below the point of the elbows. In a hydraulic seat, with its height adjustable to 9 in. above normal, this patient would be able to reach the levers more comfortably.

For Closer Approach and Transfer Sideways

1

2

3

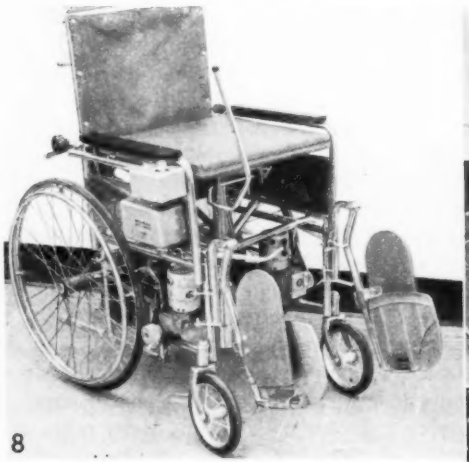
For Closer Approach and Transfer Forward

6a

6b

For Transfer Backward

For Adjustment in Height



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Following publication of the last article in this series in next month's issue, combined reprints of the series will be available on request to Dr. Edward W. Lowman, Institute of Physical Medicine and Rehabilitation, 400 East 34th Street, New York 16.

Medical Progress in 1960

MORRIS FISHBEIN*

Chicago

MUCH of current medical research is directed toward genetics, biochemistry, new surgical technics, and studies of the as yet unknown causation of several diseases.

Genetics

More than 300 hereditary metabolic disorders have been described, including such conditions as absence of pigment from the body, pancreatic fibrosis, diabetes, gout, phenylketonuria, sickle-cell anemia, and various disorders of the red coloring matter of the blood. Conceivably, muscular dystrophy, hemophilia and many diseases in which there are deficiencies of certain enzymes in the body are also genetic.

Within the cells of the living body are chromosomes which carry the hereditary characteristics. The normal number is 46. One chromosome determines the sex of the body as it develops. Investigators found that an extra, small chromosome, which may be split off from one of the ordinary chromosomes, may be responsible for mongolism. Men with inadequate genital function have been found to have an extra female chromosome, a total of 47 instead of the usual 46. In another disorder one chromosome may be missing. In such cases, female bodies are produced in which the ovaries fail to develop; these people have only 45 chromosomes. Sensitivity to drugs such as primaquine phosphate and the fava bean may be due to a genetically determined deficiency of an enzyme concerned in red-cell glucose metabolism. Many other new types of disturbances are now being related to abnormal chromosome patterns.

Autoimmunity

A person may be sensitized to his own tissues. This may explain certain forms of anemia, in which the red blood cells are destroyed, and thrombocytopenia, in which the body destroys its own blood platelets. Since cortisone-type drugs have been found successful in certain allergic diseases, attempts are now being made to attack these diseases by the administration of these corticosteroids. On the assumption that psoriasis, a disease of the skin of unknown origin, may represent such an abnormal sensitization as has been described, attempts are being made to control

*Contributing Editor, POSTGRADUATE MEDICINE; Medical Editor, "Britannica Book of the Year."

psoriasis by injecting a corticosteroid called triamcinolone triacetate directly into or adjacent to the lesions of psoriasis. The method is being tried also in certain cases of chronic eczema and in prolonged, severe acne.

Hypertension and Coronary Thrombosis

Extensive research is leading to confirmation of the opinion that a diet high in animal fats, associated with a higher percentage of cholesterol in the blood, is a basic cause of hardening of the arteries, and that hypertension, which is associated with a narrowing of the blood vessels, leads to the formation of clots and to coronary thrombosis. Dietary control can result in a low cholesterol. A search has been made for other ways of lowering the cholesterol, leading to the use of fats such as corn oil and cottonseed oil rather than butter and lard.

A new drug called triparanol has been established as useful in lowering cholesterol.[1] Some investigators feel that the attack on this problem by the use of drugs is not as scientific as the lowering of cholesterol through reduction of obesity and diminution of the animal fats in the diet. This drug inhibits the body's own production of cholesterol. However, sufficient cholesterol remains to fulfill the needs that the body has for this substance. Research has shown that it will increase the exercise tolerance in patients with angina pectoris. Its place of action seems to be in the liver, and regular tests of liver function are desirable while the drug is being taken. It is not to be administered during pregnancy because of the important part that cholesterol plays in the development of the fetus.

Investigators in the department of surgery at the Johns Hopkins Hospital, Baltimore,[2] have developed a new technic for massaging the heart through the chest wall and restoring its function when it has stopped, as sometimes occurs after a surgical procedure. In this technic, one hand of the person applying the massage is placed over the other hand, with the bottom of the lower hand resting crosswise near the lower end of the breastbone. The other hand rests on the wrist of the lower hand and points upward to the top of the breastbone. Firm pressure is then applied vertically, with a downward thrust about once per second. The hands are lifted slightly at the end of the stroke to permit full expansion of the chest. Such massage has been continued for periods of up to an hour and 10 minutes without any evidence of harm to the heart or the chest. This maneuver forces blood out of the heart and permits it to fill again with relaxation of the pressure.

Surgery of the heart continues to be advanced by scientific investigations and the development of new devices. Hypothermia permits reduction of body temperature to about 30° C., and the heart can be stopped for 8 to 10 minutes. Further cooling results in ventricular fibrillation, but this does not take place if an artificial heart is combined with a heat exchanger. With such a technic, the temperature can be dropped to about 15° C., and the heart arrested for periods approaching one hour.

One new approach has been the performance of operations on the heart under a microscope so that the tiny, delicate structures may be seen more easily. Operations have been performed on the coronary blood vessels with this technic. In Houston, Dr. Michael DeBakey and his associates have developed a technic for operating on blood vessels to remove clots that obstruct them, and technics have been developed for using plastic materials to route the blood around a clotted portion of a blood vessel.

According to studies made at the University of Pennsylvania School of Medicine, cigarette smoking speeds the clotting of blood and increases the toughness of the clot.

In epidemiologic studies carried on by a combined program of the Chicago Board of Health and the Chicago Heart Association, investigations were made of white and Negro workers in the Chicago gas company. A higher rate of obesity and of high blood pressure was considered to account for the higher rate of coronary heart disease among the Negroes studied. Research also has established the fact that too little physical exercise can lead to coronary heart disease. Workers who are quite

sedentary have a higher incidence of coronary heart disease than do those who are more active.

New drugs for the treatment of hypertension include bretylium tosylate and guanethidine. The former blockades the sympathetic nervous system at nerve endings. Guanethidine reduces sympathetic nerve activity without blockading the parasympathetic nervous system. These drugs are new tools which may be used with others already available for attacking hypertension at various links in the chain of events in the body that lead to high blood pressure. Modifications of chlorothiazide or DIURIL® which inhibit the effect of potassium loss during fluid elimination are becoming available.

Another new discovery is an artificial pacemaker for use in disorders of the nervous mechanism of the heart. The device which has been developed includes transistors and an electrode, all minute in size. The electrode is placed immediately into the heart by a rather minor surgical procedure. One elderly man already has worn such a device for six years, and the United States Veterans Administration has records of six persons who are now wearing such artificial pacemakers in order to sustain life.

Leukemia

At the annual meeting of the American Society of Hematology,[3] four authorities discussed the possible causative mechanisms of leukemia, which are now undergoing the most intensive investigation. These are viruses, radiation, hormones or chemicals, and genetic or hereditary influence. Experimental evidence was offered in support of each of these possible causes. A vote was taken among the experts. Three indicated their belief that viruses are the chief cause of leukemia; 26 thought radiation was responsible; 14 believed chemicals or hormones were the causative mechanisms; and 15 said that hereditary influences were responsible. In an overwhelming number of cases any specific cause was not even suspected.

In aplastic anemia the bone marrow is apparently unable to continue its work, and all forms of blood cells are greatly decreased in number. In patients observed at the Children's Hospital and at the Harvard Medical School, Boston, administration of a combination of glandular substances, including testosterone, the male sex hormone, and cortisone from the adrenal glands, resulted in great improvement in the red blood cells and a lesser improvement in the white blood cells and the blood platelets. In other investigations, bone-marrow substance has been placed directly into the body by transplantation and has been found to exert a favorable effect; this procedure has sometimes been used to tide the patient over the critical period.

In a conference on blood clotting held in 1960 at the Henry Ford Hospital, Detroit, a new substance was announced which is exceedingly powerful in producing clotting of the blood. In some cases of hemophilia with excessive bleeding, the blood-clotting time was reduced from 20 minutes to 28 seconds. The new blood-clotting substance is called autoprothrombin and it was isolated at the Wayne State University College of Medicine, Detroit.

Cancer

Temporary remissions and definite improvement occurred in 12 of 23 patients with cancer of the testes who were treated with methotrexate. Dr. Selman Waksman isolated an antibiotic called actinomycin D, which is injected directly into the veins. Although this agent is effective, it also is exceedingly toxic, and it can be used only with the greatest of caution. At Memorial Center for Cancer and Allied Diseases, New York, the Children's Medical Center, Boston, and the Roswell Park Memorial Institute, Buffalo, studies are being made of the effectiveness of actinomycin D and radiation in the treatment of Wilms's tumor. The drug has proved to have a definite anticancer effect.

The Russians have developed a chemotherapeutic substance called sarcolysine, which is also effective in tumors of the testes but not in other types of tumor. Leading investigators in the study of cancer are becoming more and more convinced that there will not be a single

substance specific against all forms of cancer but, more likely, different types of substance for different cancers.

Gastroenterology

A new device, the endoradio sound, is a small, readily swallowed capsule containing the mechanism for measuring local conditions, as well as a tiny transistor transmitting apparatus and a tiny battery. A radio receiver, about 6 by 4 by 3 in., placed near the patient, directly records the message or passes the impulses to a recording drum for graphic reproduction. It is possible to determine the pH, temperature, electric conductivity, enzymes and chloride-ion concentration of the juice in the stomach or small intestine.

In adults with various intragastric conditions, including ulcer or suspected cancer, the electronic method revealed illuminating findings, often of diagnostic importance. When this procedure was used in 10 patients with known gastric cancer, it showed that in those with consistent anacidity the tumor was always in the middle, in the fundic area, or toward the pylorus. In cases in which the pylorus or cardia had been excised, valuable information was obtained postoperatively on the reaction of the intestinal juices.

The endoradio sound method has the advantage of giving the physician his results at the time of the examination, without any laboratory delay, and it is much less objectionable to the patient than is a stomach tube.

The Rheumatoid Factor

When the blood of people with rheumatoid arthritis is investigated, a substance called the rheumatoid factor is found in from 70 to 95 per cent of patients. At Mount Sinai Hospital, New York, investigators found this factor three to four times more often in the blood of relatives of people with rheumatoid arthritis than among the general population. Twice as many women as men had the rheumatoid factor.

New Drugs

Among the new antibiotics are such agents as CYCLAMYCIN®, colimycin, vancomycin, DECLOMYCIN® and paromomycin (HUMATIN®). One of the most important announcements was the discovery of an antibiotic called STAPHCILLIN®, which inhibits the penicillinase which the resistant *Staphylococcus* elaborates as a defense against penicillin.[4]

Another new drug is metronidazole, which was first found in France and later fully tested in England[5] as Flagyl. This product taken by mouth is apparently effective against *Trichomonas*. Investigators in Liverpool and Glasgow[6, 7] reported that even with no local treatment the organs were dry, discharge absent, and the condition controlled by the seventh day of treatment with this agent taken orally.

For fungous infections, such drugs as MYCOSTATIN®, FUNGIZONE® (amphotericin B) and griseofulvin (FULVICIN® and GRIFULVIN®) have been found specific against various mycetes.

Several new antimalarial drugs which seem more potent than any heretofore used are undergoing investigation, and new remedies have been found for use against various infestations by worms, particularly pinworms.

The Fifth International Congress on Poliomyelitis, which met in Copenhagen, July 1960, heard discussions of new vaccines against poliomyelitis by the leading proponents of the killed vaccine (Jonas Salk) and the attenuated live oral vaccine (Albert Sabin). Russian investigators presented a mass of evidence in behalf of orally administered vaccines. The evidence was clear that the killed vaccine produces 80 per cent effectiveness against paralytic poliomyelitis. Health officers from countries in South America, Asia and Africa were convinced that the relative cheapness of the oral vaccine would make it more popular in such countries. A new, more effective killed virus vaccine, PURIVAX®, has been developed, which apparently requires only two doses instead of the three doses formerly used. The United States Public Health Service approved the use of orally administered vaccines, which are expected to become available in quantity in the United States later this year.

A formula called METRECAL® has been developed which is a well-designed combination

of protein, vitamins and mineral salts taken as a flavored drink; four doses provide 900 calories daily. The widespread use of this product has led to the marketing of innumerable imitations under a variety of trade names.

A technic for giving men the appearance of having spent a few weeks in the sunlight at the seashore was provided by a chemical called dihydroxyacetone (MAN-TAN®). Expectation was that this agent would be useful in the condition called vitiligo, in which portions of the skin are unpigmented. Unfortunately, the use of the remedy in some instances produced areas which were much more pigmented than the surrounding skin.

Nobel Prize

In 1960 the Nobel prize in medicine was awarded to Sir Frank MacFarlane Burnet, Melbourne, Australia, and Professor Peter Brian Medawar, London, for study of tissue reactions of the body. From these studies, information was gained as to why grafts of organs and of skin do not become effective. Fraternal twins, Medawar found, accept grafts of skin from each other but reject grafts from unrelated donors or parents. The research of these investigators may be an important step toward the development of a technic for making successful transplantation of organs and tissues of the body. Their studies also will contribute to an understanding of autoimmunity, in which the body may react against its own tissues.

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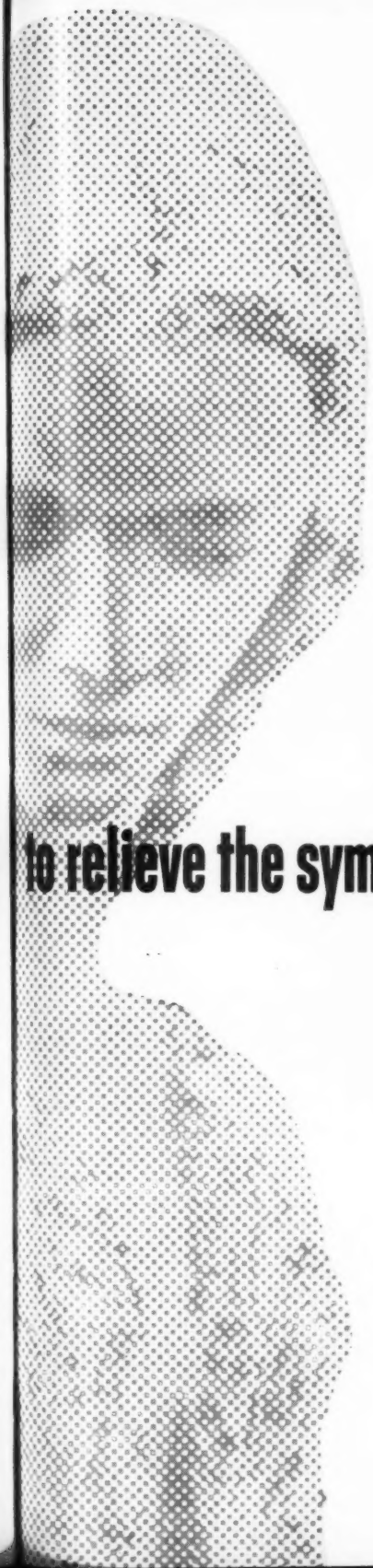

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HYDRODIURIL® WITH MEPROBAMATE
HYDROCHLOROTHIAZIDE

to relieve the symptoms of premenstrual tension

for EDEMA . . . CYCLEX provides the prompt diuresis of HYDRODIURIL for rapid reduction of weight gain, breast fullness, abdominal congestion

for MOOD-CHANGES . . . CYCLEX supplies the effective relief of meprobamate for nervousness, irritability, tension, nausea, malaise, insomnia

for GI DISTRESS . . . CYCLEX affords quick-acting relief of nausea and bloating associated with premenstrual tension

SUPPLIED: Tablets, bottles of 100. Each tablet contains 25 mg. of HYDRODIURIL (hydrochlorothiazide) and 200 mg. of meprobamate.

DOSAGE: Usual adult dosage is one tablet once or twice a day, beginning on the first morning of symptoms and continuing until the onset of menses. CYCLEX may be continued through the menstrual period.

Before prescribing or administering CYCLEX, the physician should consult detailed information on use accompanying package or available on request.

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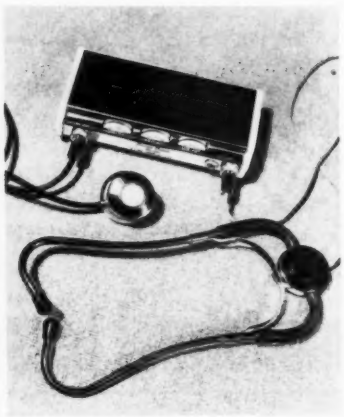

• PRIMO SCOPE (Model ES-330)

DESCRIPTION: Providing amplification up to 100 times greater than the conventional stethoscope. this lightweight, portable stethoscope features transistorized circuitry. High and low electronic filters eliminate unwanted sounds, yet they can be tuned for normal or balanced tone. Six standard Penlite cells provide power for up to six months of daily use. An auxiliary output feeds the audio signal to a tape recorder, oscilloscope or electrocardiograph; the headset and output may be used simultaneously. A leather case with shoulder strap is provided for carrying the stethoscope.
PRODUCER: Primo Sound Research Ltd., Tokyo. Japan. Distributed by Trans-Pacific Electronics. Inc., North Hollywood, Calif.

• RADIO-HIPPURAN® STERILE SOLUTION (I^{131})

DESCRIPTION: For use in studies of kidney function. Radio-Hippuran is radio-iodohippurate sodium (I^{131}). Because it is quickly cleared from the blood by the kidneys, differences between the kidneys are magnified and time required for the test procedure is reduced. The solution is administered intravenously (0.4 μc per kilogram of body weight). Each milliliter contains 0.2 to 1.5 μc I^{131}; specific activity is from 0.2 to 0.5 μc per milligram, and the concentration of Hippuran is 1 to 3 mg. per milliliter. This pyrogen-free agent is available in rubber-stoppered, 0.10 to 10 μc vials.
PRODUCER: Abbott Laboratories, North Chicago. Manufactured by Radio-Pharmaceutical Laboratories, Oak Ridge, Tenn.

• ISOPTO® CARPINE 6% (New Formula)

PURPOSE: To treat glaucoma and other conditions in which miosis is desired.
COMPOSITION: A sterile solution of 6 per cent pilocarpine hydrochloride in a 0.5 per cent methylcellulose vehicle.
CAUTION: This agent should not be used in conditions in which miotics are either undesirable or contraindicated.
DOSAGE AND ADMINISTRATION: 1 or 2 drops every four hours on advice of physician.
HOW SUPPLIED: 15 cc. DROP-TAINER® dispensers.
PRODUCER: Alcon Laboratories, Inc., Fort Worth.

(Continued on page A-100)

asleep minutes after

This is the promise of Noludar 300... a night of deep, refreshing sleep without risk of habituation or toxicity... 6 to 8 hours of undisturbed rest... an easy awakening in the morning, free of fogginess or barbiturate "hangover." Try Noludar 300 for your next patient with a sleep problem. One capsule at bedtime. Chances are she'll tell you

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• ABBEON THERMOMETER (Model TAB-8)

DESCRIPTION: Operated by metallic element, this wall-mounted thermometer records temperatures from –30° F. to +230° F. within 1 per cent of accuracy over the entire range. The instrument is in a brass case and is 2½ in. deep with an overall diameter of 7¾ in. The dial is 6½ in. in diameter.
PRODUCER: Abrax Instrument Corporation, Jamaica, N. Y.

• OBES TT®

PURPOSE: To provide anorectic action and nutritional support in weight control.
COMPOSITION: Each TEMPOTROL® tablet contains 15 mg. d-amphetamine sulfate and eight vitamins.
CAUTION: This drug is contraindicated in myocardial or coronary disease, hypertension and hyperthyroidism. Insomnia may result if the tablet is not taken early in the day.
DOSAGE AND ADMINISTRATION: 1 tablet on arising.
HOW SUPPLIED: Bottles of 30 and 500.
PRODUCER: Columbus Pharmacal Company, Columbus, Ohio.

• DERMA-BRITE

PURPOSE: To treat dermatoses.
COMPOSITION: Sulfur, zinc sulfate, zinc oxide and bithionol.
INDICATIONS FOR USE: Acne, seborrheic dermatitis, tinea corporis and tinea versicolor.
DOSAGE AND ADMINISTRATION: Apply lotion topically and allow to dry before removing excess.
PRODUCER: Amulet Laboratories, Inc., Glenside, Pa.

• DALCA®

PURPOSE: Symptomatic relief of colds, hay fever and sinus congestion.
COMPOSITION: Each tablet contains:

Aluminum aspirin	300 mg.
Phenylephrine hydrochloride	10 mg.
Chlorpheniramine maleate	2 mg.
Phenindamine tartrate	5 mg.

CAUTION: This drug should not be given in more than the recommended dosage or administered to children less than six years old. Persons with high blood pressure, heart disease, diabetes or thyroid disease should use this drug only as directed. If drowsiness results, the patient should not drive a car or operate machinery.
DOSAGE AND ADMINISTRATION: For adults, 1 tablet, to be repeated in four hours if necessary; the dosage should not exceed 4 tablets in 24 hours. For children 7 to 12 years old, one-half the adult dosage.
HOW SUPPLIED: Bottles of 100 and 500.
PRODUCER: B. F. Ascher & Company, Inc., Kansas City, Mo.

• ACTIFED-C® EXPECTORANT

PURPOSE: Antitussive, antihistaminic, decongestive and bronchodilative therapy.
COMPOSITION: Each 5 cc. of syrup contains:

Codeine phosphate	10 mg.
ACTIDIL® (triprolidine hydrochloride)	2 mg.
SUDAFED® (pseudoephedrine hydrochloride)	30 mg.
Glyceryl guaiacolate	100 mg.

CAUTION: Some patients may note side effects of mild stimulation or mild sedation. Pseudoephedrine hydrochloride should be administered with caution to hypertensive patients. Triprolidine hydrochloride may produce drowsiness, and appropriate precautions should be observed.
DOSAGE AND ADMINISTRATION: The following doses are to be administered four times daily: for adults and for children more than 12 years old, 2 teaspoonfuls; for children 6 to 12 years old, 1 teaspoonful; for infants and for children less than six years old, ½ teaspoonful. For a more frequent dosage schedule, administer one-half the recommended dose every three hours.
HOW SUPPLIED: 1 pt. bottles.
PRODUCER: Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N. Y.

(Continued on page A-102)

Metamine®
(trolnitrate phosphate, Leeming, 10 mg.)
Sustained

in coronary insufficiency

helps you dilate the coronaries

In pharmacologic studies at Pasteur Institute and McGill University, the vasodilator activity of trolnitrate phosphate (METAMINE) was found to be equal or superior to that of nitroglycerin, and of much longer duration.[1-2]

In coronary insufficiency, one METAMINE SUSTAINED tablet q. 12 h. markedly reduces the number and severity of anginal attacks and increases exercise tolerance, with virtual freedom from nitrate side effects and less danger of a forgotten dose.[3-4] Bottles of 50 and 500 tablets.

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1 tablet all day

1 tablet all night

• METAHYDRIN®

PURPOSE: Diuretic therapy.
COMPOSITION: Trichlormethiazide.
CAUTION: Electrolyte depletion may occur if maximal dosage is continually used. This agent is contraindicated in complete renal failure, increasing azotemia and development of hyperkalemia or acidosis in severe renal disease.
DOSAGE AND ADMINISTRATION: Orally, according to severity of the condition and the patient's response.
HOW SUPPLIED: 2 or 4 mg. tablets in bottles of 100 and 1000.
PRODUCER: Lakeside Laboratories, Milwaukee.

• ORATROL®

PURPOSE: To treat glaucoma.
COMPOSITION: Each tablet contains 50 mg. dichlorphenamide.
CAUTION: If side effects characteristic of carbonic anhydrase inhibitors occur, the dosage should be reduced or the drug temporarily discontinued.
DOSAGE AND ADMINISTRATION: For adults, 2 to 4 tablets initially, followed by 2 tablets every 12 hours until desired response is obtained; for maintenance therapy, ½ to 1 tablet one to three times daily.
HOW SUPPLIED: Bottles of 100.
PRODUCER: Alcon Laboratories, Inc., Fort Worth.

• CORTISPORIN® OPHTHALMIC SUSPENSION

PURPOSE: To treat ophthalmic conditions.
COMPOSITION: Each cubic centimeter contains:

AEROSPORIN® (polymyxin B sulfate)	10,000 units
Neomycin sulfate	5 mg.
Hydrocortisone (1%)	10 mg.

These agents are suspended in a sterile saline vehicle, isotonic with tears.
CAUTION: This agent is not recommended for the treatment of dendritic ulcers (herpes corneae) or conditions involving the posterior segment of the eye. Prolonged use may result in the overgrowth of nonsusceptible organisms.
DOSAGE AND ADMINISTRATION: Instill 1 to 2 drops in the affected eye every three or four hours. Use more frequently in acute conditions if required.
HOW SUPPLIED: 5 cc. bottles with sterile dropper.
PRODUCER: Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N. Y.

• VOLEMETRON

DESCRIPTION: Providing determinations accurate to better than 5 per cent, this instrument can be used without modification for all blood volume measurements. After radioactive-labeled material has been injected into the blood stream and mixed evenly in the circulation, a blood sample is obtained and its radioactivity determined. The volume in which the material has been diluted can then be calculated. The total time required for a determination is 10 to 15 minutes. Prepackaged doses, supplied with disposable syringes and sample tubes, are available. The unit weighs 200 lb., measures 35¼ by 38 by 22 in., and is mounted on a steel cart with a bumper.
PRODUCER: Perkin-Elmer Corporation, Norwalk, Conn.

• TENUATE® DOSPAN®

PURPOSE: Prolonged control of hunger.
COMPOSITION: Each tablet contains 75 mg. diethylpropion.
INDICATIONS FOR USE: Any condition in which progressive weight loss is desirable through reduced caloric intake and in obesity complicated by cardiovascular disease, diabetes or pregnancy.
CAUTION: Characteristic reactions to this type of drug may be presented by sensitive patients.
DOSAGE AND ADMINISTRATION: 1 tablet per day in midmorning.
HOW SUPPLIED: Bottles of 100.
PRODUCER: The Wm. S. Merrell Co., Cincinnati.

• ENDURON®

PURPOSE: Diuretic therapy.
COMPOSITION: Methyclothiazide.
CAUTION: Serum electrolytes should be watched. If weakness, nausea, lassitude or cramps appear, the dosage should be lowered or the drug withdrawn. Enduron should be used with caution in patients already under treatment with other hypotensive drugs, particularly ganglion-blocking agents.
DOSAGE AND ADMINISTRATION: 2.5 to 10 mg. daily. If edema proves resistant to Enduron alone, the concomitant administration of an aldosterone inhibitor or a glucocorticoid may be of value.
HOW SUPPLIED: 2.5 or 5 mg. tablets in bottles of 100 and 1000.
PRODUCER: Abbott Laboratories, North Chicago.

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COMMENTS FROM THE REPORTS

effective in long-term weight reduction

"A significant percentage of [105] overweight patients followed a formula-diet [Metrecal] regimen for substantial periods of time.... It is impressive that the average weight loss was 6.2 pounds in the first week, 4.5 pounds in the second week, 3.7 pounds in the third week and then 2.1 to 3.5 pounds per week from the fourth through the sixteenth week."[1]

in simple weight reduction

"The weight loss achieved with the use of Metrecal as the sole source of calories—in most of our subjects approximately one-half pound per day—is consistent with health and encourages the patient to persevere in the dietary reduction of obesity."[2]

in seriously ill obese patients

Metrecal has been used in overweight patients with serious medical disorders such as: diabetes mellitus requiring insulin therapy; advanced stages of coronary and hypertensive heart disease; peptic ulcer; cirrhosis of the liver, and extensive rheumatoid arthritis requiring steroid therapy. Weight losses ranged from 1 to 12 pounds the first week (average 6.3 pounds) with satisfactory weight losses thereafter. No significant complications were encountered.[3]

METRECAL[T.M.] BRAND

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provides adequate nutrition

The 900-calorie daily Metrecal diet provides 70 Gm. protein plus vitamins and minerals to meet or exceed Minimum Daily Requirements. Over ⅔ of the 20 Gm. of fat content in the daily ration consists of unsaturated fatty acids (Iodine number: 90). Cholesterol value low: 25 mg.

Available in powder and liquid in a variety of flavors

references: (1) Tullis, I. F.; Allen, C. E., and Overman, R. R.: Simple Effective Weight Reduction: A Clinical Study, Scientific Exhibit, 6th Internat. Cong. Int. Med., Basel, Switzerland, Aug. 24-27, 1960. (2) Antos, R. J.: The Use of a New Dietary Product (Metrecal) for Weight Reduction, Southwestern Med. *40*:695-697 (Nov.) 1959. (3) Roberts, H. J.: Effective Long-Term Weight Reduction—Experiences with Metrecal, accepted for publication.

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THE MEDICAL Bookman

► OBSTETRICS

By J. P. Greenhill, M.D., Senior Attending Obstetrician and Gynecologist, Michael Reese Hospital, Chicago. Ed. 12. 1,098 pages with 1,219 illustrations, 119 in color. 1960, W. B. Saunders Company, Philadelphia and London. $17.00.

In this edition of De Lee's "Obstetrics," the author carries forward with renewed vigor a work which was initiated during the previous five editions, and includes within the present text contributions from outstanding authors working within the field of obstetrics. This volume covers some of the most recent data on the physiology and biochemistry of the placenta, endocrinologic changes that occur in pregnancy, newer concepts of the mechanism of labor, roentgenographic data, and physiologic disorders of the heart, gastrointestinal tract, lungs, eyes, ears, nose and throat. Additional chapters are devoted to pathologic conditions in the newborn.

The entire format of the textbook has been changed from that of previous editions, and many new illustrations have been included.

E. A. B.

► DEAFNESS

By John Chalmers Ballantyne, F.R.C.S., Consultant Ear, Nose and Throat Surgeon, Royal Free Hospital and Royal Northern Hospital, London, England. 254 pages with 71 illustrations. 1960, Little, Brown & Company, Boston. $8.00.

The basic information related to hearing, hearing loss, deafness and rehabilitation is briefly covered in this monograph. The text is presented in seven sections, dealing with the structure of the ear, applied acoustics and physiology; the diagnosis of deafness; hearing aids; the principles underlying the management of conduction deafness; perception deafness; psychogenic deafness, and the handicap of deafness from the standpoint of the psychologic aspects and rehabilitation. Some of the appendixes are concerned with testing materials for use in audiology clinics, word and sentence lists, and a listing of the audiology clinics in Great Britain.

L. R. B.

► HEART CARE
An Authoritative Guide by Twenty Experts

Edited by Morris Fishbein, M.D., Medical Editor, Britannica Book of the Year. 246 pages, illustrated. 1960, Hanover House, Garden City, New York. $2.95.

In this exceptionally fine book written for the laity, the subject of heart disease is treated intelligently and clearly. The contributors are internationally known experts on cardiovascular disease. A note of optimism for the future of the patient with heart disease is present throughout the monograph. Controversial subjects pertaining to cardiovascular disease have been handled fairly. The format of the book is good, and there is very little repetition in the various chapters.

This monograph will prove valuable to every cardiac patient, to his friends, and to his family, and will lead to a better understanding of matters relating to cardiovascular diseases.

J. F. B.

(Continued on page A-148)

ILOPAN®

to prevent...to relieve... post-op distention and ileus

Surgical stress appears to increase the body's pantothenic acid requirements. ILOPAN (d-pantothenyl alcohol, W-T) provides additional pantothenic acid to aid restoration of normal peristalsis. Clinical studies and hundreds of case histories[1, 2] attest the effectiveness of ILOPAN against postoperative retention of flatus and feces — even paralytic ileus — and in reducing the need for intestinal intubation, or the period of intubation.

ILOPAN may be used with a high degree of safety — is not contraindicated even under conditions of mechanical bowel obstructions, produces no hyper-peristalsis or cramping, no side effects — and can be routinely administered by the nurse.

2 cc. AMPULS
(500 mg.)
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1. Kareha, L. G., de Quevedo, N. G., Tighe, P., Kehrli, H. J., "Evaluation of Ilopan in Postoperative Abdominal Distention," Western J. Surg. Obs. & Gyn., 66:220, 1958.
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WARREN-TEED PHARMACEUTICALS

► CARDIAC EMERGENCIES AND RELATED DISORDERS
Their Mechanism, Recognition and Management

By Harold D. Levine, M.D., Senior Associate in Medicine, Peter Bent Brigham Hospital, Boston. 381 pages, illustrated. 1960, Landsberger Medical Books, Inc., New York. $12.00.

In this practical and informative book, the common and uncommon emergencies which the physician may be called on to handle are described in excellent detail. The differential diagnosis of such conditions is also covered.

The text includes discussions of acute left ventricular failure, cardiogenic shock, chest pain, refractory congestive heart failure, electrolyte disturbances, digitalis intoxication, arrhythmias, cardiac syncope, and cardiac arrest and resuscitation. The recent report on closed-chest cardiac massage was published too late for inclusion.

The appropriate forms of treatment of the conditions described are given detailed presentation. A good bibliography accompanies the text.

D. C. C.

Books received are acknowledged in this department. As space permits, books of principal interest to our readers will be reviewed more extensively. Additional listings will be found on pages 116 and 123 of this issue.

Clinical Applications of Bronchology. By Dezso Kassay, M.D., Professor of Bronchoesophagologic Research, Temple University School of Medicine, Philadelphia. 225 pages, illustrated. 1960, The Blakiston Division, McGraw-Hill Book Company, Inc., New York, Toronto and London. $15.00.

Occupational Diseases and Industrial Medicine. By Rutherford T. Johnstone, M.D., Clinical Professor of Preventive Medicine and Public Health, University of California, Los Angeles, and Seward E. Miller, M.D., Director, Institute of Industrial Health, University of Michigan, Ann Arbor. 482 pages, illustrated. 1960, W. B. Saunders Company, Philadelphia and London. $12.00.

Pseudomonas Aeruginosa Infections. Modern Medical Monographs. By Claude E. Forkner, Jr., M.D., Assistant in Medicine, Cornell University Medical College, New York. 104 pages, illustrated. 1960, Grune & Stratton, Inc., New York and London. $5.25.

Diabetes Mellitus; a Clinical and Pathological Study of 2,529 Cases. American Lecture Series. By E. T. Bell, M.D., Emeritus Professor of Pathology, University of Minnesota Medical School, Minneapolis. 67 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $3.75.

The Year Book of General Surgery (1960-1961). Edited by Michael E. DeBakey, M.D., Professor of Surgery and Chairman, Cora and Webb Mading Department of Surgery, Baylor University College of Medicine, Houston. 616 pages, illustrated. 1960, The Year Book Publishers, Inc., Chicago. $8.00.

Neoplastic Disease at Various Sites. A Clinical Prospect of the Cancer Problem. By D. W. Smithers, M.D., Professor of Radiotherapy, University of London Faculty of Medicine, London. Introductory volume. 232 pages, illustrated. 1960, E. & S. Livingstone Ltd., Edinburgh and London. Distributed by The Williams & Wilkins Company, Baltimore. $8.50.

Diagnostic Roentgenology of the Digestive Tract Without Contrast Media. By Bernard S. Wolf, M.D., Director, Department of Radiology, Mansho T. Khilnani, M.B., Associate Fellow in Radiology, and Arthur Lautkin, M.D., Associate Radiologist, Mount Sinai Hospital, New York. 180 pages, illustrated. 1960, Grune & Stratton, Inc., New York and London. $8.75.

Cirrhosis of the Liver. By Martin Seler Kleckner, Jr., M.D., Assistant Clinical Professor of Medicine (Gastroenterology), Vanderbilt University School of Medicine, Nashville. 729 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $24.50.

The Christian as a Doctor. By James T. Stephens, M.D., and Edward LeRoy Long, Jr., Associate Professor of Religion, Oberlin College, Oberlin, Ohio. 121 pages. 1960, Association Press, New York. $2.50.

The Year Book of Obstetrics and Gynecology (1960-1961). Edited by J. P. Greenhill, M.D., Senior Attending Obstetrician and Gynecologist, Michael Reese Hospital, Chicago. 576 pages, illustrated. 1960, The Year Book Publishers, Inc., Chicago. $8.00.

The Sturge-Weber Syndrome. By G. L. Alexander, M.D., Surgeon in Charge, Department of Neurological Surgery, Frenchay Hospital, and R. M. Norman, M.D., Research Consultant in Neuropathology, Southwestern Regional Hospital Board, Bristol, England. 95 pages, illustrated. 1960, John Wright & Sons Ltd., Bristol. Distributed by The Williams & Wilkins Company, Baltimore. $7.50.

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Abstracts of Japanese Medicine. Abstracts of the medical literature of Japan in the clinical and theoretical fields. Edited by T. Yoshida, Dean, Tokyo University Faculty of Medicine, Tokyo, and J. Huizinga, Amsterdam. Vol. 1. No. 1. 188 pages. 1960, Excerpta Medica Foundation, Amsterdam, London and New York. $30.00 per year for 12 issues.

Lectures on Haematology. Edited by F. G. J. Hayhoe, M.D., University of Cambridge Faculty of Medicine, Cambridge, England, with 13 contributors. 247 pages, illustrated. 1960, Cambridge University Press, London and New York. $11.50.

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*Barber, T.E.: Ind. Med. & Surg. 28:54 (Feb.) 1959.

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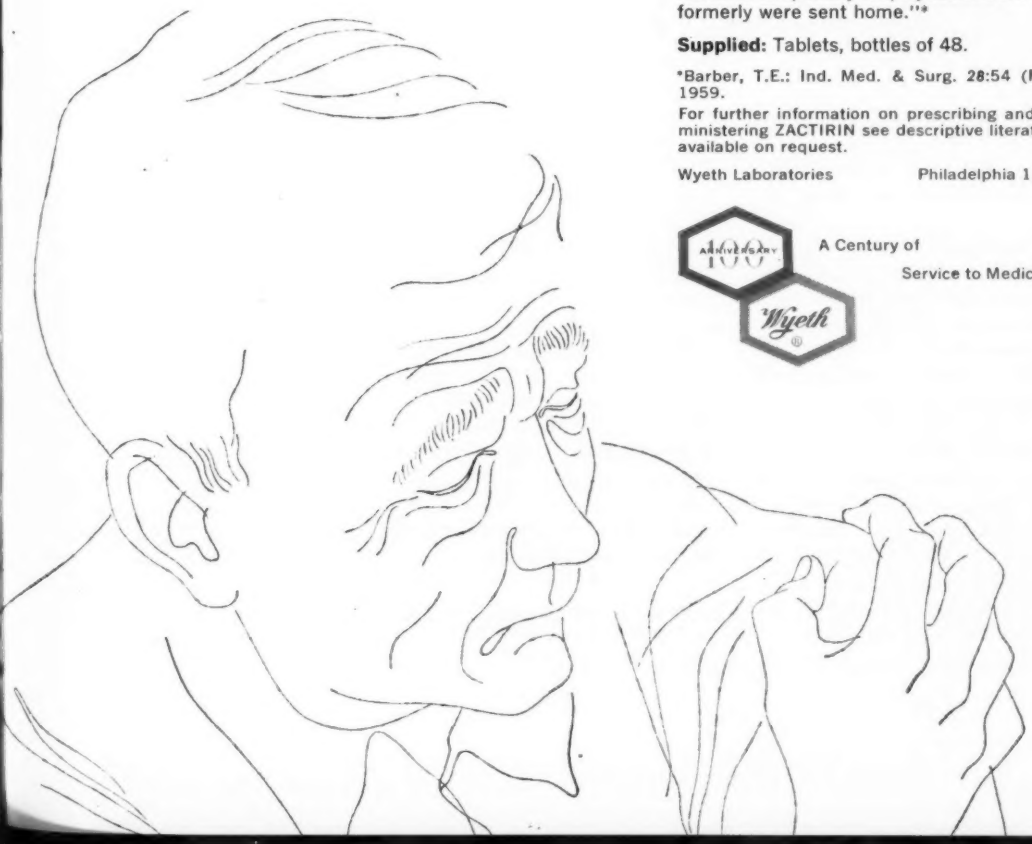


A Century of Service to Medicine

DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Nov. 1—To the home of Rabbi Louis Mann to meet Rabbi Schwartz and other officers of the Forum, and then to Sinai Temple to participate in a symposium with Joseph Block of Inland Steel and General Wilbur on "Our national purpose."

Nov. 2—By jet to New York and to the Waldorf. Next to the RCA Club for luncheon with Bill Lasdon, Bill White and Max Geffen and for a journalistic discussion. Afterward to Bill Lasdon's office to meet some research men concerned with problems of pain in the back. Later to dine at "21" and then to see Menasha Skulnik in a play called "The 49th Cousin," full of humor and too close to reality in some spots to be funny. And after that to Lindy's for *Kranzkuchen* and coffee.

Nov. 3—To breakfast came Bill White and next to meet with H. B. Parmele and others on the problems of pathology related to tobacco. At noon came Mark Soroko to luncheon and after that Bill Marsden and Ellwood Douglass to work out more programs for *World-Wide Abstracts*. To dine at the Marco Polo Club with Janet Kern and Mrs. Pepys, and then to see the play based on John Hersey's novel, "The Wall," which is a heart-rending depiction of the great disaster of the Warsaw ghetto in the war.

Nov. 4—To Doubleday's for a conference with Milton Runyon and Richard Whittemore and picked up some light reading for the plane. Thereafter to visit the new home of the American Friends of the Hebrew University, conferring here with Zelda Popkin and Nisselson, and later came Dr. Blum from Minneapolis. At night to dine lightly at the Savarin and then to see "The Best Man," a play by Gore Vidal of modern politics dealing with the presidential nomination.

Nov. 5—All morning at the desk and watched a wonderful high school football game while reading "Rabbit, Run" by John Updyke, which is modern writing with high flavor and intimate psychology. At noon to the Plaza for luncheon with Herbert and Grace Mayes, and then back to watch Army and Syracuse play at football while playing "Scrabble" with Mistress Pepys. Later came Mark Soroko and the Franks and with them to dine at the Marco Polo Club. To the theater to see Meredith Willson's "The Unsinkable Molly Brown," which is amusing and full of music like that of "The Music Man." When Harry Truman entered the audience with his wife, daughter and son-in-law, great excitement ensued, everyone standing to watch his quiet entrance.

Nov. 6—By the morning jet from Idlewild to O'Hare and from there to the South Side of Chicago on the new Northwest Highway in 40 minutes. In the afternoon watched the Baltimore Colts demonstrate their usual proficiency and then to dine with Barbara and all her family.

Nov. 7—All this day at the desk and in the evening with Acting Chancellor Wendell (Pat) Harrison and his lady to the Tower Club to dine, and then to hear "La Bohème."

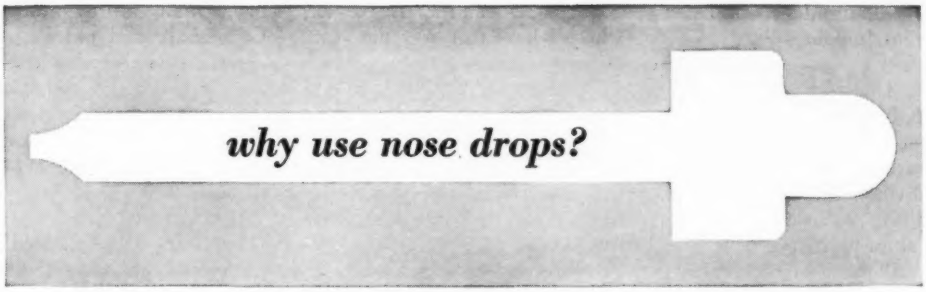
Nov. 8—Election Day and the polls were packed with prospective voters. Early to speak for the Nurses' Workshop of the Chicago Heart Association, where as usual Miss Courtenay provided an early morning audience of more than 700. In the evening to see the returns come in, reading meanwhile a novel by Nicholas Monsarrat, "The Nylon Pirates."

Nov. 10—At the desk, reading meanwhile "The Last of the Just" by André Schwarz-Bart, a winner of the Goncourt prize in France, recounting the drama of the pogroms and the destruction of the Jewish people in Europe throughout the ages. This is a story beautifully written and moving the reader to anguish. This evening with Mistress Pepys to the Symphony Orchestra where Hans Rosbaud conducted.

Nov. 11—To visit Mr. Wildman, gossiping with him about younger days in Indiana and telling him of medicolegal problems. In the evening to a tremendous dinner given by Roland and Henrietta Frieder at the Standard Club. At the table with Dr. Harold Goldburgh of Philadelphia, and Charles Kann and his lady, and here were all of the old crowd who still remain, including Helen Kahn, who is about to celebrate her sixtieth birthday and looks a pretty 35.

Nov. 12—At the desk and watched a magnificent football game in which Iowa defeated Ohio State handily. In the evening to the Parsons' home where among the guests were my old

(Continued on page A-152)



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chums William Meyers and Pauline from Indianapolis.

Nov. 13—In the afternoon to the Art Institute to see the beautiful exhibit of Corot's paintings. Thereafter to visit Grandma Mantel who is most happy at 92. In the evening heard a magnificent lecture by Nelson Glueck on the significance of the new archaeological findings in Israel.

Nov. 14—At my desk and read the newly arrived autobiography of Abe Willinsky of Toronto. And his life was fascinating in its rise from the new immigrant family to scientific leadership in his field. In the afternoon a considerable discussion with Rabbis Elefant and Novick on how to promote still further the translations of Maimonides. In the evening with Justin and Ann to the Tower Club to dine and then to hear what is the premier performance of the Lyric Opera season—Tebaldi, Gobbi, Giuseppe di Stefano, Mariano Caruso and others in "Tosca."

Nov. 15—By the morning plane to Des Moines, reading en route "It's Cheaper to Die" by William Mitchelfelder, which purports to be a serious muckraking attack on the American Medical Association, but becomes instead a rather inaccurate requotation of all the various newspaper controversial discussions which have appeared in the last few years. At Des Moines with Charles A. Haney, motoring to Marshalltown, Iowa, and there with the Reverend Buchmueller, superintendent, touring the Evangelical Hospital. At night came a thousand people to discuss the program for rehabilitation and additions to the hospital, and I was happy indeed to see my old friends Drs. Robert Hansen, R. S. Grossman and E. L. Keyser, whom I have met over the years at many medical meetings. Afterward came Dr. O. D. Wolfe and his mother and old Pepys reminisced of the time when we traveled to South America together in 1935. Then back to Des Moines and on the Rock Island to Chicago.

Nov. 16—In the evening with Dr. Razim to the Riverside Country Club and spoke there for the annual opening dinner of the Douglas Park Branch of the Chicago Medical Society.

Nov. 17—Early came Sylvia Covet for some hours of planning on POSTGRADUATE MEDICINE. At noon to the annual meeting of the Chicago Heart Association where a citation was presented to Nathaniel Leverone of the Automatic Canteen Company of America, who has aided greatly the campaign against heart disease, and then Willis Potts presented to old Pepys the Distinguished Achievement Award of the American Heart Association together with a citation, and it was for old Pepys a thrilling occasion.

In the evening to meet with the nominating committee of the American Medical Writers' Association, where came Austin Smith, Van Antwerp, Ev Lyght, Ted Van Dellen and Harold Swanberg. Next to the Bismarck Hotel to hear George Barr preside and open the Easter Seal campaign, and old Pepys spoke at some length on the future of the handicapped.

Nov. 18—Early to the meeting of the American Medical Writers' Association where Austin Smith and Ted Van Dellen welcomed the guests. In the evening citations were given to Barry J. Anson, Edward R. Pinckney, Dean Smiley and Lowell Coggeshall, and old Pepys rendered a long-overdue tribute to Harold Swanberg, who against terrible odds and at great sacrifice built this organization from its initial eight members to more than 1500.

Nov. 19—Early indeed to the conference on effective medical writing and here were excellent talks by Walter Kahoe, W. D. Snively, Jr., Selma DeBakey, T. Jerome Enright, Jr. and Dr. Joseph Garland. Next was another symposium with Justus Schifferes, old Pepys, Dick Hewitt and Walter Alvarez, and in the midst of this came the sad news of the death of Dr. Laurance D. Redway, editor of the *New York State Journal of Medicine*, who would have been a participant in this symposium.

In the evening with Mistress Pepys to the home of Consul General and Mrs. G. C. D. Hooft Graafland of the Netherlands, after which to the home of Jay and Adele Herz in Winnetka and here found conversation with Bob Hart, Lou Maison, the Brandts and many others.

Nov. 20—At noon to Chicago's new exposition hall, on the lake at 23rd Street, and already conceded to be the greatest of its kind. So dining in its immense cafeteria, and after that to view the household show.

Nov. 21—A day of correspondence and conferences, then in the evening with Herbert and Ethel Rattner and Jay Herz and his lady to dine at the Tower Club, and thereafter to hear what the critics say is the greatest performance of Wagner's "Die Walküre" ever presented in the Lyric Opera or anywhere.

(Continued on page A-154)

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Nov. 22—In the morning to participate in the program of Don McNeill. In the evening to hear the famous J. B. Priestley at the Sinai Forum tell of his despair at the way in which the world is going nowadays.

Nov. 24—Thanksgiving Day and enjoyed it with all the family, the Sam Hoffmans, the Samuel Mantels, and the Thomas Mantels, making about 28 people for dinner.

Nov. 25—Early awake to find the mail profuse, and this day began to read the amazing book by William L. Shirer called "The Rise and Fall of the Third Reich," which is the definitive work on an epoch in history so terrifying that it seems inconceivable.

Nov. 27—Sitting at home with a cold and still reading Shirer and watching football in Denver amidst a terrific storm. At night to dine with the Friedells and played at bridge with Mistress Pepys as my partner, and though we delight in our uniformity in many other things, in this game we somehow never seem to get together.

Nov. 28—At noon to the Chicago Heart Association where my Public Health Education Committee met and designed new exhibits for fairs and for the Museum of Science and Industry, prospected the preparation of new educational material, and looked particularly into the teaching of health in the Chicago public schools which seems sadly deficient. In the evening with the Jay Herzes and the Louis Manns for some remarkable food at the Bohemia Cafe which is opposite Union Station. Thereafter to hear sung "Madame Butterfly" with Leontyne Price.

Nov. 29—A cold winter day, the first of the season. In the evening to the Guildhall of the Ambassador West, and there met Bishop Sheil, Dr. John Sheinin and Neison Harris for photographs and interviews. After that a great banquet at which all spoke and then the subscriptions for the Chicago Medical School were announced and they totaled almost $1 million.

Nov. 30—At noon to the Blackstone where the Citizens Board of the University of Chicago met for luncheon and heard Daniel J. Boorstin, professor of history, speak of the American image. In the afternoon more conferences on the new translations of Maimonides. Still reading "The Rise and Fall of the Third Reich," and finding it ever more fascinating and marveling more and more at the scholarship of William Shirer, its author.

The Medical Muse

RICHARD ARMOUR

ELECTRONIC SECRETARY

An electronic secretary enables doctors at the new Palo Alto-Stanford Hospital Center to dictate reports at any hour in the night.—*News item.*

Punch a button, switch a switch,
And though you have a nervous twitch
And droopy eyelids, reddish eyes,
Your thoughts go down. Then what surprise,

What consternation to behold
The sheet of typing, neat and cold,
That says you said the things you said
When you were half (three-quarters) dead.

The electronic secretary
Will never leave you, never marry,
And will record, if so you wish,
Each syllable of gibberish.

SNORE STUDY

According to research reported by the British Medical Association, women are more easily cured of snoring than men, since most women snore with their mouths open and therefore respond more readily to treatment. —*News item.*

Most women snore with mouths ajar,
And therefore can be cured.
Quite frankly we admit we are,
On this point, reassured.

What bothers us is what is said
Of men, to whom wives listen,
A scarf wrapped tight about their head,
Their face with cream aglisten.

If with mouth closed, as it is found,
A man perversely snores,
How does he make that dreadful sound—
Could it be through his pores?